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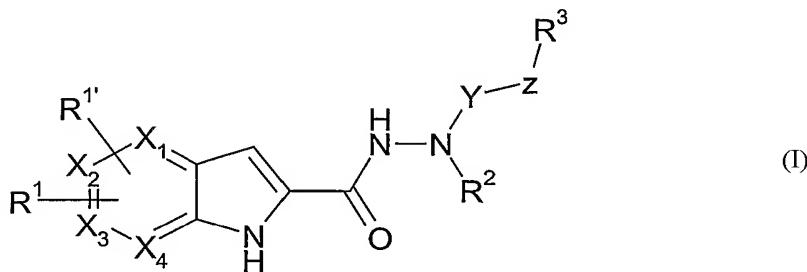
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(54) Title: PYRROLOPYRIDINE-2-CARBOXYLIC ACID HYDRAZIDES



(57) Abstract: Compounds of Formula (I): or pharmaceutically acceptable salts thereof, are inhibitors of glycogen phosphorylase and are useful in the prophylactic or therapeutic treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia e.g. myocardial ischemia, or as cardioprotectants or inhibitors of abnormal cell growth.

WO 2005/085245 A1

PYRROLOPYRIDINE-2-CARBOXYLIC ACID HYDRAZIDES AS INHIBITORS OF GLYCOGEN PHOSPHORYLASE

BACKGROUND OF THE INVENTION

The present invention is directed to pyrrolopyridine-2-carboxylic acid hydrazides. In particular, the present invention is directed to pyrrolopyridine-2-carboxylic acid hydrazides that are inhibitors of glycogen phosphorylase.

Insulin dependent Type I diabetes and non-insulin dependent Type II diabetes continue to present treatment difficulties even though clinically accepted regimens that include diet, exercise, hypoglycemic agents, and insulin are available. Treatment is patient dependent therefore there is a continuing need for novel hypoglycemic agents, particularly ones that may be better tolerated with fewer adverse effects.

The liver and certain other organs produce glucose (thereby raising the blood sugar level) by breaking down glycogen or by synthesizing glucose from small molecule precursors. The breakdown of glycogen is catalyzed by glycogen phosphorylase enzyme. Accordingly, inhibiting glycogen phosphorylase ("GP") may lower the elevated blood sugar level in diabetic patients.

Similarly, hypertension and its associated pathologies such as, for example, atherosclerosis, lipidemia, hyperlipidemia and hypercholesterolemia have been associated with elevated insulin levels (hyperinsulinemia), which can lead to abnormal blood sugar levels. Furthermore, myocardial ischemia can result. Such maladies may be treated with hypoglycemic agents, including compounds that inhibit glycogen phosphorylase. Accordingly, it is accepted that compounds that inhibit glycogen phosphorylase (see, for example, U.S. Patent No. 6,297,269) are useful in the treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, atherosclerosis or myocardial ischemia. Nevertheless, it would be desirable to obtain other novel compounds that inhibit glycogen phosphorylase.

R. Kurukulasuriya, J.T. Link, et al., *Current Medicinal Chem.*, 10:99-121(2003) describes "Prospects for Pharmacologic Inhibition of Hepatic Glucose Production." R. Kurukulasuriya, J.T. Link, et al., *Current Medicinal Chem.*, 10:123-153(2003) describes "Potential Drug Targets and Progress Towards Pharmacologic Inhibition of Hepatic Glucose Production."

U.S. Patent No. 6,297,269 and European Patent No. EP 0832066 describes substituted *N*-(indole-2-carbonyl)amides and derivatives as glycogen phosphorylase inhibitors. U.S. Patent Nos. 6,107,329 and 6,277,877 describe substituted *N*-(indole-2-carbonyl)glycinamides and derivatives as glycogen phosphorylase inhibitors. U.S. Patent No. 6,399,601 describes bicyclic pyrrolyl amides as glycogen phosphorylase inhibitors. International Patent Publication No. WO 03/037864 describes indole derivatives as glycogen phosphorylase inhibitors. European Patent Application Nos. EP 0978276 and EP 1136071 describe inhibitors of human glycogen phosphorylase and their use. International Patent Publication No. WO 01/68055 describes glycogen phosphorylase inhibitors. U.S. Patent No. 5,952,322 describes a method of reducing non-cardiac ischemial tissue damage using glycogen phosphorylase inhibitors.

European Patent Application No. EP1177791 describes the use of glycogen phosphorylase inhibitors to inhibit abnormal cell growth, e.g. in the treatment of cancer and hyperproliferative disorders.

International Patent Publication No. WO 04/104001 (published after the priority date of the present application) discloses pyrrolopyridine-2-carboxylic acid amide inhibitors of glycogen phosphorylase.

International Patent Publication No. WO 04/113345 (published after the priority date of the present application) discloses fused pyrrole compounds as inhibitors of glycogen phosphorylase.

International Patent Publication No. WO 01/55146 describes arylamidines. International Patent Publication No. WO 01/62775 describes antiarrhythmic peptides. International Patent Publication No. WO 01/96346 describes tricyclic compounds. International Patent Publication No. WO 02/16314 describes substituted polyamine compounds. International Patent Publication No. WO 02/20475 describes serine protease activity inhibitors. International Patent Publication No. WO 02/40469 describes bombesin receptor antagonists. International Patent Publication No. WO 02/46159 describes guanidine and amidine derivatives. International Patent Publication No. WO 00/69815 describes ureido-substituted cyclic amine derivatives.

International Patent Publication No. WO 00/43384 describes aromatic heterocyclic compounds. International Patent Publication Nos. WO 02/26697 and WO 00/76970 describe aromatic derivatives. International Patent Publication No. WO 01/32622 describes indoles. European Patent Application No. EP 1101759 describes phenylazole compounds. European Patent Application No. EP 1179341 describes cyclic amino compounds. U.S. Patent No. 6,037,325 describes substituted heterocyclic compounds. U.S. Patent No. 5,672,582 describes 4-substituted cyclohexylamine derivatives. European Patent Application No. EP 1201239 describes cyclic amine CCR3 antagonists. International Patent Publication No. WO 98/25617 describes substituted arylpiperazines. U.S. Patent No. 5,756,810 describes preparing 3-nitro benzoate compounds.

U.S. Patent No. 5,710,153 describes tetrazole compounds. U.S. Patent Nos. 6,174,887 and 6,420,561 describe amide compounds. S.P. Hiremath et al., *Acta Ciencia Indica*, XVIII:397(1992) describes the synthesis and biological activities of indolylthiosemicarbazides and semicarbazides. International Patent Publication No. WO 96/36595 describes 3,4-disubstituted phenylsulfonamides. U.S. Patent No. 5,618,825 describes combinatorial sulfonamide libraries. European Patent Application No. EP 0810221 describes oxygen-containing heterocyclic derivatives. European Patent Application No. 0345990 describes polypeptide compounds. European Patent Application No. 0254545 describes diamine compounds.

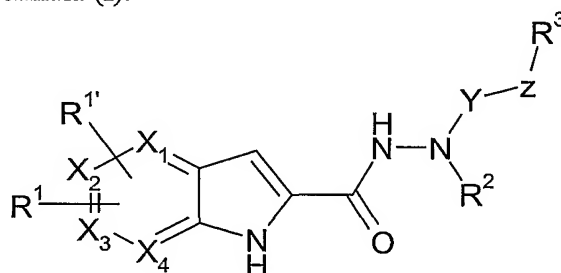
International Patent Publication No. WO 97/31016 describes inhibitors of SH2-mediated processes. U.S. Patent No. 6,034,067 describes serine protease inhibitors. International Patent Publication No. WO 97/17985 and U.S. Patent No. 6,107,309 describe hemoregulatory compounds. U.S. Patent No. 6,432,921 describes thrombin inhibitors. U.K. Patent Application No. GB 2292149 describes peptide inhibitors of pro-interleukin-1 β converting enzyme. U.S. Patent No. 5,821,241 describes fibrinogen receptor antagonists.

International Patent Publication No. WO 01/02424 describes peptide boronic acid compounds. U.S. Patent Nos. 6,001,811, 5,869,455 and 5,618,792 describe oxadiazole, thiadiazole and triazole peptoids. U.S. Patent Nos. 5,885,967, 6,090,787 and 6,124,277 describe thrombin inhibiting peptide derivatives. U.S. Patent No. 6,455,529 describes adhesion receptor antagonists. U.S. Patent No. 6,410,684 describes serine protease inhibitors.

International Patent Publication No. WO 01/94310 describes bis-heterocyclic alkaloids. U.S. Patent Publication No. 20030004162A1, European Patent Application No. EP 0846464 and International Patent Publication No. WO 96/39384 describe glycogen phosphorylase inhibitors. International Patent Publication No. WO 97/28798 describes pyrrolidine derivatives. U.S. Patent No. 5,346,907 describes amino acid analogs.

SUMMARY OF THE INVENTION

Compounds of formula (I):

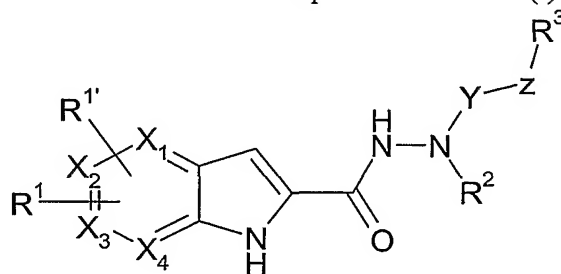


I

or pharmaceutically acceptable salts thereof, are inhibitors of glycogen phosphorylase and are useful in the prophylactic or therapeutic treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia e.g. myocardial ischemia, or as cardioprotectants or inhibitors of abnormal cell growth.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I):



I

or a pharmaceutically acceptable salt thereof, wherein:

one of X₁, X₂, X₃ and X₄ is N and the others are C;

Y is -C(O)-, -S(O)₂-, or -C(NH)-;

Z is C₁₋₄alkylene, oxygen, -(CH₂)_mO-, -O(CH₂)_m-, -NR-, -(CH₂)_mNR-, -NR(CH₂)_m-, -(CH₂)_mS(O)₂-, or a bond;

m is 1, 2, 3, or 4;

R is C₀₋₄alkyl, C₀₋₄alkylaryl, or C₀₋₄alkylhetaryl;

R¹ and R^{1'} are each independently, halogen, hydroxy, cyano, C₀₋₄alkyl, C₁₋₄alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, or ethynyl;

R² is C₀₋₄alkyl, COOR⁶, COR⁶, C₁₋₄alkoxyC₁₋₄alkyl-, hydroxyC₁₋₄alkyl-, cycloalkylC₀₋₄alkyl-, arylC₀₋₄alkyl-, or hetarylC₀₋₄alkyl-, wherein any of the aryl or hetaryl rings are optionally substituted with 1-2 independent halogen, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, -N(C₀₋₄alkyl)(C₀₋₄alkyl), -SO₂C₁₋₄alkyl, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents;

R³ is hydrogen, -COOC₀₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkyl, arylC₁₋₄alkylthio-, -C₀₋₄alkylaryl, -C₀₋₄alkylhetaryl, -C₀₋₄alkylcycloalkyl, or -C₀₋₄alkylheterocyclyl, wherein any of the rings is optionally substituted with 1-3 independent halogen, cyano, C₁₋₄alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, -C₀₋₄alkylNHC(O)O(C₁₋₄alkyl), -C₀₋₄alkylNR⁷R⁸, -C(O)R⁹, C₁₋₄alkoxyC₀₋₄alkyl-, -COOC₀₋₄alkyl, -C₀₋₄alkylNHC(O)R⁹, -C₀₋₄alkylC(O)N(R¹⁰)₂, -C₁₋₄alkoxyC₁₋₄alkoxy, hydroxyC₀₋₄alkyl-, -NHSO₂R¹⁰, -SO₂(C₁₋₄alkyl), -SO₂NR¹¹R¹², 5- to 6-membered heterocyclyl, phenylC₀₋₂alkoxy, or phenylC₀₋₂alkyl substituents, wherein phenyl is optionally substituted with 1-2 independent halogen, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, -N(C₀₋₄alkyl)(C₀₋₄alkyl), -SO₂C₁₋₄alkyl, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents, or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo (=O) substituent;

or R³ is -NR⁴(-C₀₋₄alkylR⁵);

R⁴ is C₀₋₃alkyl, -C₂₋₃alkyl-NR⁷R⁸, C₃₋₆cycloalkyl optionally substituted by hydroxyC₀₋₄alkyl- further optionally substituted by hydroxy, C₁₋₂alkoxyC₂₋₄alkyl-, or C₁₋₂alkyl-S(O)_n-C₂₋₃alkyl-;

n is 0, 1, or 2;

R⁵ is hydrogen, hydroxyC₂₋₃alkyl-, C₁₋₂alkoxyC₀₋₄alkyl-, or aryl, hetaryl, or heterocyclyl;

wherein a heterocyclic nitrogen-containing R⁵ ring optionally is mono-substituted on the ring nitrogen with C₁₋₄alkyl, benzyl, benzoyl, C₁₋₄alkyl-C(O)-, -SO₂C₁₋₄alkyl, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), C₁₋₄alkoxycarbonyl, or aryl(C₁₋₄alkoxy)carbonyl; and wherein the R⁵ rings are optionally mono-substituted on a ring carbon with halogen, cyano, C₁₋₄alkyl-C(O)-, C₁₋₄alkyl-SO₂-, C₁₋₄alkyl, C₁₋₄alkoxy, hydroxy, -N(C₀₋₄alkyl)(C₀₋₄alkyl), hydroxyC₀₋₄alkyl-, or C₀₋₄alkylcarbamoyl-, provided that no quaternised nitrogen is included; or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo (=O) substituent;

R⁶ is C₁₋₄alkyl, aryl, or hetaryl;

R⁷ and R⁸ are independently C₀₋₄alkyl, C₃₋₆cycloalkyl, or CO(C₁₋₄alkyl);

R⁹ is C₁₋₄alkyl, or C₃₋₆cycloalkyl;

R¹⁰ is C₀₋₄alkyl, or C₃₋₆cycloalkyl; and

R¹¹ and R¹² are independently C₀₋₄alkyl or together with the nitrogen to which they are attached may form a 4- to 6-membered heterocycle;

provided there are no nitrogen-oxygen, nitrogen-nitrogen, oxygen-oxygen or nitrogen-halogen bonds in the grouping -Y-Z-R³.

The molecular weight of the compounds of formula (I) is preferably less than 800, more preferably less than 600.

X₃ is preferably N.

Y is preferably -C(O)- or -S(O)₂-.

Z is preferably a C₁₋₄alkylene, oxygen, -(CH₂)_m-, -NR- or a bond. More preferably Z is a bond.

R is preferably C₀₋₄alkyl.

R¹ and R^{1'} are preferably each independently, hydrogen, halogen or cyano. More preferably one of R¹ and R^{1'} is hydrogen and the other is halogen, e.g. chloro. More preferably one of R¹ and R^{1'} is hydrogen and the other is 5-chloro.

R² is preferably C₀₋₄alkyl. More preferably R² is hydrogen.

R³ is preferably hydrogen, -NR⁴(-C₀₋₄alkylR⁵), aryl, hetaryl, or heterocyclyl wherein any of the rings is optionally substituted as described above for formula (I).

R⁴ is preferably hydrogen.

Specific compounds of the invention which may be mentioned are those included in the examples and pharmaceutically acceptable salts thereof.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in formula (I) is selected from the preferred, more preferred, most preferred, especially or particularly listed groups for each variable. Therefore, this invention is intended to include all combinations of preferred, more preferred, most preferred, especially and particularly listed groups.

As used herein, unless stated otherwise, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

As used herein, for example, "C₀₋₄alkyl" is used to mean an alkyl having 0-4 carbons — that is, 0, 1, 2, 3, or 4 carbons in a straight or branched configuration. An alkyl having no carbon is hydrogen when the alkyl is a terminal group. An alkyl having no carbon is a direct bond when the alkyl is a bridging (connecting) group.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and include mono-, bi-, and tricyclic saturated carbocycles, as well as fused and bridged systems. Such fused ring systems can include one ring that is partially or fully unsaturated, such as a benzene ring, to form fused ring systems, such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl and carbocyclic rings include C₃₋₁₀cycloalkyl, e.g. C₃₋₈cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and decahydronaphthalene, adamantane, indanyl, 1,2,3,4-tetrahydronaphthalene and the like.

The term "halogen" includes fluorine, chlorine, bromine, and iodine atoms.

The term "aryl" is well known to chemists. The preferred aryl groups are phenyl and naphthyl, especially phenyl.

The term "hetaryl" is well known to chemists. The term includes 5- or 6-membered heteroaryl rings containing 1-4 heteroatoms chosen from oxygen, sulfur, and nitrogen in which oxygen and sulfur are not next to each other. Examples of such heteroaryl rings are furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

The term "hetaryl" includes hetaryl rings with fused carbocyclic ring systems that are partially or fully unsaturated, such as a benzene ring, to form a benzofused hetaryl. For example, benzimidazole, benzoxazole, benzothiazole, benzofuran, quinoline, isoquinoline, quinoxaline, and the like.

Unless otherwise stated, the terms "heterocyclic ring" and "heterocyclyl" are equivalent, and include 4–8-membered saturated or partially saturated rings containing one or two heteroatoms chosen from oxygen, sulfur, and nitrogen. The sulfur and oxygen heteroatoms are not directly attached to one another. Any nitrogen heteroatoms in the ring may optionally be substituted with C₁₋₄alkyl. Examples of heterocyclic rings include azetidine, oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocane, thietane, thiazolidine, oxazolidine, oxazetidine, pyrazolidine, isoxazolidine, isothiazolidine, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, *N*-methylpiperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, homopiperazine, morpholine, thiomorpholine, 1,2,3,6-tetrahydropyridine and the like. Other examples of heterocyclic rings include the oxidized forms of the sulfur-containing rings. Thus, tetrahydrothiophene-1-oxide, tetrahydrothiophene-1,1-dioxide, thiomorpholine-1-oxide, thiomorpholine-1,1-dioxide, tetrahydrothiopyran-1-oxide, tetrahydrothiopyran-1,1-dioxide, thiazolidine-1-oxide, and thiazolidine-1,1-dioxide are also considered to be heterocyclic rings. The term "heterocyclic" also includes fused ring systems and can include a carbocyclic ring that is partially or fully unsaturated, such as a benzene ring, to form benzofused heterocycles. For example, 3,4-dihydro-1,4-benzodioxine, tetrahydroquinoline, tetrahydroisoquinoline and the like.

Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above formula (I) is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of formula (I) and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When a tautomer of the compound of formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically drawn or stated otherwise.

When the compound of formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric,

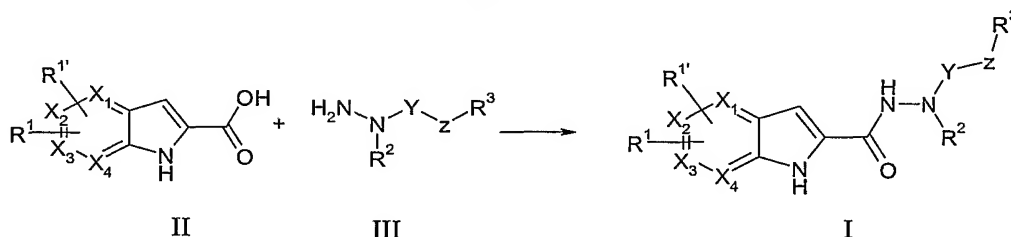
ferrous, lithium, magnesium, potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, *p*-toluenesulfonic acid and the like.

Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure especially at least 98% pure (% are on a weight for weight basis).

The compounds of formula (I) can be prepared as outlined in Scheme 1 below wherein R^1 , $R^{1'}$, R^2 , R^3 , X_1 , X_2 , X_3 , X_4 , Y and Z are as defined above for formula (I):

Scheme 1



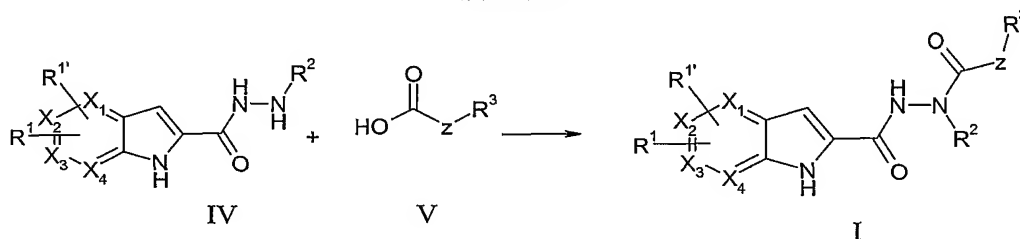
According to Scheme 1, the compounds of formula (I) may be prepared by coupling the appropriate pyrrolopyridine-2-carboxylic acid of formula (II) with the appropriate hydrazide of formula (III), wherein $Y = C(O)$. Compounds of formula (II) can be obtained by the synthesis described in Scheme 7 below. Compounds of formula (III) are generally commercially available or are readily prepared by known techniques.

Typically, the compound of formula (II) is combined with compounds of formula (III) in the presence of a suitable coupling agent. Examples of suitable coupling reagents are 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride/hydroxybenzotriazole (EDCI / HOBt), 1,1-carbonyldiimidazole (CDI), dicyclohexylcarbodiimide/ hydroxybenzotriazole (DCC / HOBt), *O*-(1H-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (R. Knorr *et al.*, *Tetrahedron Lett.*, 1989, 30, 1927–1930) and polymer supported carbodiimide-1-hydroxybenzotriazole (for representative procedures, see for example, Argonaut Technical Note 501 available from Argonaut Technologies, Inc., Foster City, California).

The couplings are performed in an inert solvent, preferably an aprotic solvent at a temperature of about 0°C to about 45°C for about 1 to 72h in the presence of a tertiary amine base such as diisopropylethylamine (DIPEA) or triethylamine. Exemplary solvents include acetonitrile, chloroform, dichloromethane, *N,N*-dimethylformamide (DMF) or mixtures thereof. Use of these coupling agents and appropriate selection of solvents and temperatures are known to those skilled in the art or can be readily determined from the literature. These and other exemplary conditions useful for coupling carboxylic acids are described in Houben-Weyl, Vol XV, part II, E. Wunsch, Ed., G. Thieme Verlag, 1974, Stuttgart, and M. Bodansky, Principles of Peptide Synthesis, Springer-Verlag, Berlin, 1984 and The Peptides, Analysis, Synthesis and Biology (Ed., E. Gross and J. Meienhofer), Vols 1-5, Academic Press NY 1979-1983.

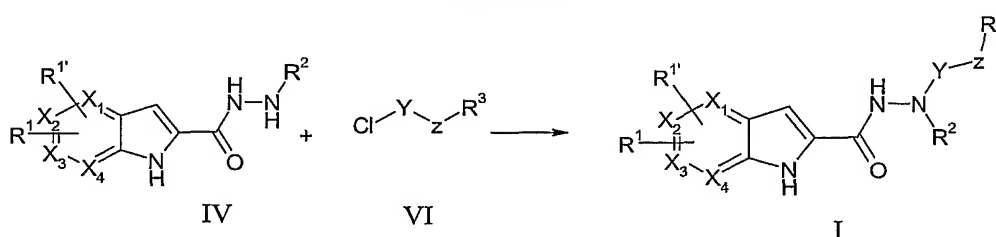
The compounds of formula (I), wherein Y is C(O), may also be prepared according to Scheme 2 by coupling the appropriate hydrazide of formula (IV) with the appropriate carboxylic acid of formula (V). Examples of suitable coupling agents and conditions are as described above. Compounds of formula (IV) can be obtained by the synthesis described in Scheme 9 below. Compounds of formula (V) are commercially available or are readily prepared by known techniques.

Scheme 2



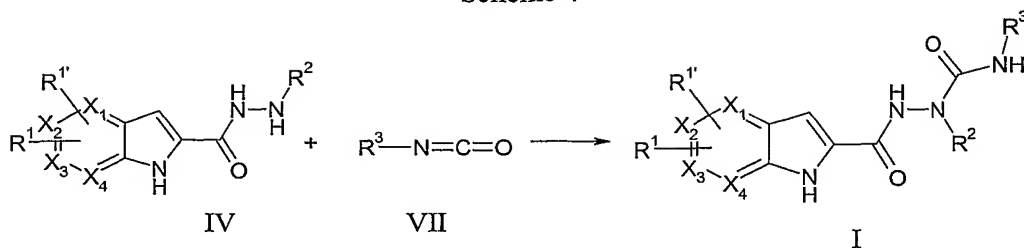
The compounds of formula (I), wherein Y is C(O) or -SO₂-, may be prepared according to Scheme 3 by mixing the appropriate hydrazide of formula (IV) with the appropriate acid chloride or sulfonyl chloride of formula (VI) in pyridine at room temperature, or alternatively in the presence of a tertiary amine base, e.g. diisopropylethylamine in a solvent such as 1,4-dioxane or THF at room temperature. Acid chlorides or sulfonyl chlorides of formula (VI) are commercially available or are readily prepared by known techniques.

Scheme 3



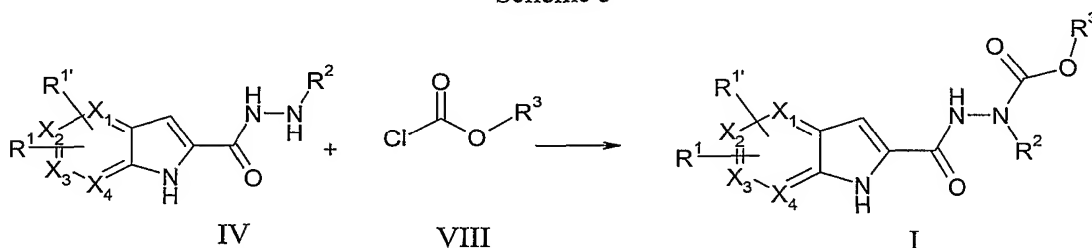
The compounds of formula (I), wherein Y is C(O) and Z is NH, may be prepared according to Scheme 4 by heating the appropriate hydrazide of formula (IV) with the appropriate isocyanate of formula (VII) under reflux in the presence of a tertiary amine base, e.g. diisopropylethylamine in a solvent such as 1,4-dioxane or toluene.

Scheme 4



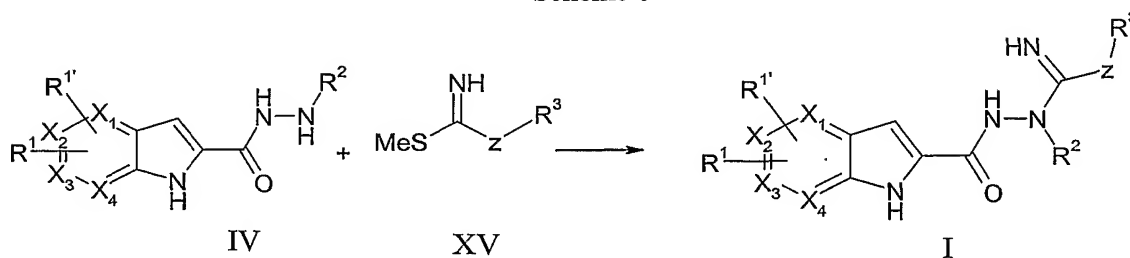
The compounds of formula (I), wherein Y is C(O), and Z is oxygen, may be prepared according to Scheme 5 by mixing the appropriate hydrazide of formula (IV) with the appropriate chloroformate of formula (VIII) in the presence of a tertiary amine base, e.g. triethylamine in a solvent such as dichloromethane.

Scheme 5

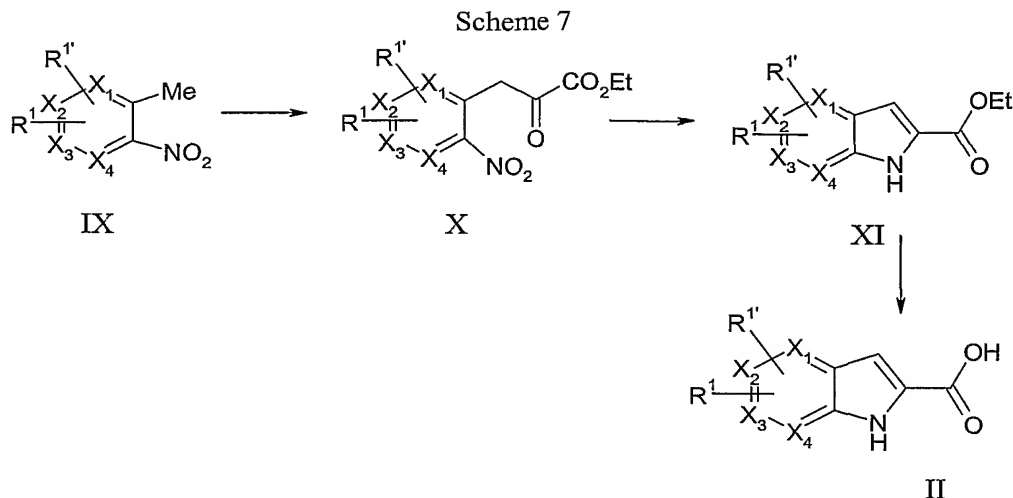


The compounds of formula (I), wherein Y is C(NH), may be prepared according to Scheme 6 by mixing the appropriate hydrazide of formula (IV) with the appropriate thioimide of formula (XV) in a solvent such as ethanol or dimethylformamide.

Scheme 6

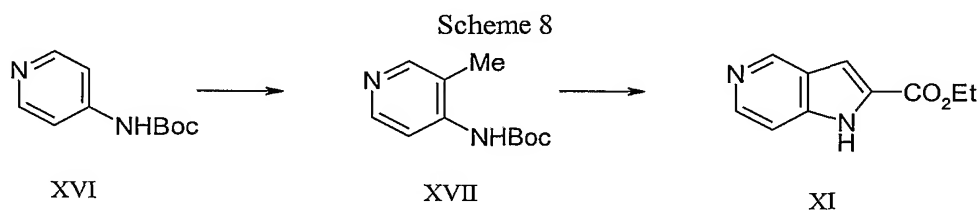


The compounds of formula (II) may be prepared according to Scheme 7. Compounds of formula (X) may be prepared by condensation of *ortho*-methyl nitro compounds of formula (IX) with an oxalate ester in a solvent such as diethyl ether in the presence of a base such as potassium ethoxide or DBU. Compounds of formula (XI) are prepared from compounds of formula (X) under reducing conditions, such as iron powder and ammonium chloride in ethanol at about 70°C, or by hydrogenation in ethanol using palladium catalysis at around 20°C. Compounds of formula (XI) undergo ester hydrolysis using aqueous alkali under standard conditions to give pyrrolopyridine-2-carboxylic acids of formula (II).



This three step process is similar to the Reissert indole synthesis (Reissert, *Chemische Berichte* **1897**, 30, 1030). Conditions for accomplishing this sequence and references thereto, are described in Kermack et al., *J. Chem. Soc.*, **1921**, 119, 1602; Cannon et al., *J. Med. Chem.* **1981**, 24, 238; and Julian et al., in *Heterocyclic compounds*, Vol 3 (Wiley, New York, NY, 1962, R.C. Elderfield, Ed. p 18).

Alternatively, the compounds of formula (XI) wherein X_2 is nitrogen can be prepared as illustrated in Scheme 8.

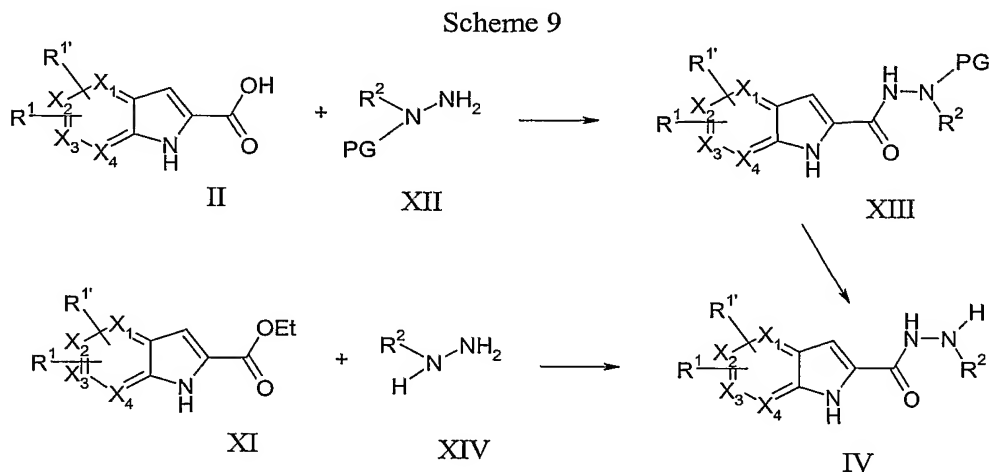


Deprotonation of compounds of formula (XVI) with an organolithium such as *n*-butyllithium in a suitable solvent such as THF, followed by quenching with methyl iodide gives compounds of formula (XVII). Such compounds can undergo further deprotonation with *tert*-butyllithium, in a suitable solvent such as THF, followed by quenching with diethyl oxalate and subsequent heating of the intermediate under reflux in hydrochloric acid, to give compounds of formula (XI).

Further details for the preparation of compounds of formula (II) can be found in WO04/104001 and the examples therein.

Formula (XIII) compounds may be prepared as described in Scheme 9 by coupling of carboxylic acids of formula (II) with hydrazines of formula (XII), wherein PG is a protecting group, e.g. Boc. Examples of suitable coupling agents and conditions are as described above for Scheme 1. Formula (IV) compounds may then be prepared by removal of the protecting group, e.g. where PG is Boc, under acidic conditions using for example trifluoroacetic acid in dichloromethane at temperatures of around 25°C. Formula (II) compounds are made as described above (Scheme 7) or are commercially available. Formula (XII) compounds are commercially available or are readily prepared by known techniques.

Alternatively compounds of formula (IV), wherein R^2 is hydrogen, may be prepared (Scheme 9) by heating an ethyl ester of formula (XI) with compounds of formula (XIV), wherein R^2 is hydrogen, in a solvent such as ethanol under reflux for a period of 3 to 24h.



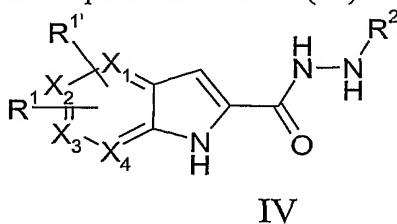
Further details for the preparation of the compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial “split and mix” approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The compounds of formulae (II) and (IV) may be protected in the 1-position e.g. with an arylmethyl, acyl, alkoxycarbonyl, sulfonyl or silyl group. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example, *Protective Groups in Organic Chemistry*, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

Any novel intermediates as defined above are also included within the scope of the invention.

The invention also provides a compound of formula (IV):



wherein R^1 , $R^{1'}$, R^2 , X_1 , X_2 , X_3 and X_4 are as defined above for formula (I), or a protected derivative thereof.

As indicated above the compounds of formula (I) are useful as inhibitors of glycogen phosphorylase, for the treatment of conditions such as diabetes, particularly Type II diabetes. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

The invention also encompasses a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by inhibiting glycogen phosphorylase, resulting in the prophylactic or therapeutic treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, e.g. myocardial ischemia, cardioprotection or inhibition of abnormal cell growth, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula (I), or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions may optionally comprise other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of formula (I), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous).

Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These

formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, diabetes and hyperglycemia may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Similarly, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, atherosclerosis or myocardial ischemia may be effectively treated, or cardioprotection or inhibition of abnormal cell growth achieved, by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of formula (I) may be used in the treatment of diseases or conditions in which glycogen phosphorylase plays a role.

Thus the invention also provides a method for the treatment of a disease or condition in which glycogen phosphorylase plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Diseases or conditions in which glycogen phosphorylase plays a role include diabetes (including Type I and Type II, impaired glucose tolerance, insulin resistance and diabetic complications such as neuropathy, nephropathy, retinopathy and cataracts), hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis, tissue ischemia e.g. myocardial ischemia, cardioprotection and abnormal cell growth e.g. cancer or hyperproliferative disorders.

The invention also provides a method for the treatment of hyperglycemia or diabetes, particularly Type II diabetes, comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the prevention of diabetes in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering to a subject in need thereof an effective prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In the treatment of diabetes, e.g. Type II diabetes, the compounds of the invention are particularly suited to night time dosing, optionally in combination with another antidiabetic agent.

The invention also provides a method for the treatment of hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, or achieving cardioprotection or inhibition of abnormal cell growth, comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the treatment of a condition as defined above.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition as defined above.

In the methods of the invention the term "treatment" includes both therapeutic and prophylactic treatment.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, may be administered alone or in combination with one or more other therapeutically active compounds. The other therapeutically active compounds may be for the treatment of the same disease or condition as the compounds of formula (I) or a different disease or condition. The therapeutically active compounds may be administered simultaneously, sequentially or separately.

The compounds of Formula (I) may be administered with other active compounds for the treatment of diabetes, for example insulin and insulin analogs, sulfonyl ureas and analogs, biguanides, α_2 agonists, fatty acid oxidation inhibitors, α -glucosidase inhibitors, β -agonists, phosphodiesterase inhibitors, lipid lowering agents, antiobesity agents, amylin antagonists, lipoxxygenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTP1B inhibitors, gluconeogenesis inhibitors, antilypolitic agents, GSK inhibitors, galanin receptor agonists, anorectic agents, CCK receptor agonists, leptin, CRF antagonists or CRF binding proteins.

The compounds of formula (I) may also be administered in combination with thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors or sorbitol dehydrogenase inhibitors.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

Materials & methods:

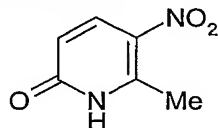
Column chromatography was carried out on SiO₂ (40–63 mesh). LCMS data were obtained using a Waters Symmetry 3.5 μ C₁₈ column (2.1 \times 30.0 mm, flow rate = 0.8 mL min⁻¹) eluting with a (5% MeCN in H₂O)–MeCN solution containing 0.1% HCO₂H over 6min & UV detection at 220nm. Gradient information: 0.0–1.2min: 100% (5% MeCN in H₂O); 1.2–3.8min: Ramp up to 10% (5% MeCN in H₂O)–90% MeCN; 3.8–4.4min: Hold at 10% (5% MeCN in H₂O)–90% MeCN; 4.4–5.5min: Ramp up to 100% MeCN; 5.5–6.0min: Return to 100% (5% MeCN in H₂O). The mass spectra were obtained employing an electrospray ionisation source in the positive (ES⁺) ion mode. Mass directed purification was performed on a Micromass Platform LC with cone voltage 30v, employing an electrospray ionisation source in the positive (ES⁺) ion mode, Waters 996 Photodiode Array Detector (210–390nm), Xterra Prep MS, C₁₈, 5 μ 19x50mm columns, and a mobile Phase of MeCN + 0.1% Formic Acid / H₂O+5%MeCN+0.1% Formic Acid. NMR spectra were acquired at 27°C on a Varian Mercury 400 spectrometer operating at 400 MHz or on a Bruker AMX2 500 spectrometer operating at 500MHz.

Abbreviations & acronyms:

CDI: 1,1-carbonyldiimidazole; DIPEA: *N,N*-Diisopropylethylamine; DMF: *N,N*-Dimethylformamide; DMSO: Dimethylsulfoxide; EDCI: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; GP: Glycogen Phosphorylase; Glc: Glucose; G6P: Glucose-6-phosphate; G6PDH: Glucose-6-phosphate dehydrogenase; HATU: *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HOBt: 1-Hydroxybenzotriazole; PS: Polymer supported; rt: room temperature; RT: Retention time; THF: Tetrahydrofuran.

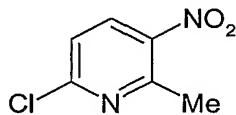
INTERMEDIATES:

Preparation 1: 6-Methyl-5-nitro-1*H*-pyridin-2-one



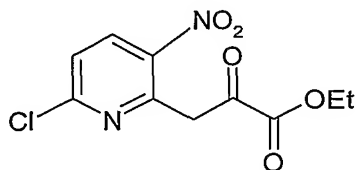
The title compound was prepared according to the method of Baumgarten and Su., (*J. Am. Chem. Soc.*, **1952**, *74*, 3828). δ_H (d₆ DMSO): 2.62 (3H, s), 6.28 (1H, d), 8.10 (1H, d).

Preparation 2: 2-Chloro-6-methyl-4-nitropyridine



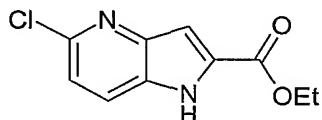
A suspension of 6-methyl-5-nitro-1*H*-pyridin-2-one (Preparation 1, 3.53g, 22.9mmol) in phosphorous oxychloride (20mL) was heated to 115°C for 3h then allowed to cool to rt. The phosphorous oxychloride was removed *in vacuo* and the residue poured into iced water (100mL). The mixture was quenched by addition of saturated sodium bicarbonate solution then the aqueous mixture was extracted with ethyl acetate (3 x 100mL). The combined organics were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo* to give the title compound. δ_H (CDCl₃): 2.86 (3H, s), 7.36 (1H, d), 8.27 (1H, d).

Preparation 3: 3-(2-Chloro-5-nitropyridin-6-yl)-2-oxopropionic acid ethyl ester



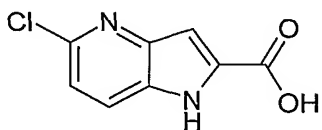
To a solution of potassium ethoxide (134mg, 1.59mmol) in diethyl ether (5mL) and ethanol (1mL) was added diethyl oxalate (218 μ L, 1.59mmol) in one portion and the resulting solution was stirred for 30min at rt. 2-Chloro-6-methyl-5-nitropyridine (Preparation 2, 250mg, 1.45mmol) was added as a suspension in diethyl ether (2mL) and stirring was continued for 17h at rt. The mixture was filtered on a sinter, washing with cold diethyl ether. The collected precipitate was dissolved in glacial acetic acid then evaporated to dryness *in vacuo* to give the title compound. δ_H (CDCl₃): 1.40 (3H, t), 4.38 (2H, q), 7.33 (1H, d), 7.37 (1H, s), 8.40 (1H, d).

Preparation 4: 5-Chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid ethyl ester



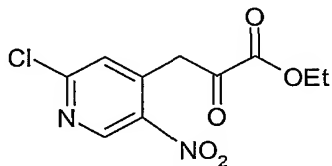
To a solution of 3-(2-chloro-5-nitropyridin-6-yl)-2-oxopropionic acid ethyl ester (Preparation 3, 1.53g, 5.6mmol) in THF (65mL) and ethanol (30mL) was added saturated aqueous ammonium chloride solution (30mL) and the suspension was vigorously stirred at rt. Iron powder (1.95g, 34.8mmol) was added portionwise and the mixture was heated under reflux for 2h then allowed to cool prior to filtration through a celite plug, and washed with warm THF. The mixture was concentrated under reduced pressure to give an aqueous suspension, which was filtered through a sinter, washing with water. The wet solid was washed with methanol and dried. The residue was adsorbed onto silica gel and purified *via* flash chromatography eluting with ethyl acetate/hexane (1:19) to give the title compound. δ_H (CD₃OD): 1.42 (3H, t), 4.42 (2H, q), 7.15 (1H, s), 7.30 (1H, d), 7.89 (1H, d); m/z (ES⁺) = 225.03 [$M + H$]⁺, RT = 3.32min.

Preparation 5: 5-Chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid



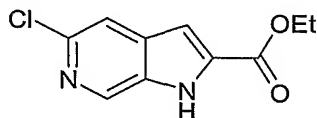
To a stirred solution of 5-chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid ethyl ester (Preparation 4, 151mg, 0.67mmol) in ethanol (10mL) was added sodium hydroxide (0.35mL, 2M) and the stirred solution was heated to 70°C for 2h. The reaction mixture was allowed to cool to rt and left to stand for 16h. The pH was adjusted to 4 by addition of glacial acetic acid, the solvents removed *in vacuo* to give a white solid, which was suspended in dichloromethane and filtered through a sinter, washing with additional dichloromethane. The filter cake was then washed with ethyl acetate (3 x 30mL) and dried to give the title compound. δ_H (CD₃OD): 6.97 (1H, s), 7.17 (1H, d), 7.83 (1H, d); m/z (ES⁺) = 197 [$M + H$]⁺; RT = 2.82min.

Preparation 6: 3-(2-Chloro-5-nitropyridin-4-yl)-2-oxopropionic acid ethyl ester



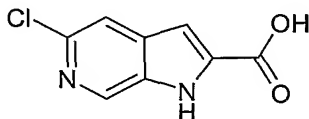
To a solution of potassium ethoxide (1.46g, 17.4mmol) in diethyl ether (80mL) and ethanol (10mL) under an argon atmosphere was added diethyl oxalate (2.4mL, 17.4mmol) and the mixture was stirred at rt for 30min. A solution of 2-chloro-4-methyl-5-nitropyridine (3.0g, 17.4mmol) in diethyl ether (20mL) was added resulting in the formation of a dark green precipitate. The reaction was stirred at rt for 15h, cooled to 0°C, filtered and washed with cold diethyl ether to give a dark green solid. The solid was dissolved in water (200mL) and acidified to pH 4 with acetic acid to give a precipitate. The solid was collected by filtration and dried to give the title compound. m/z (ES^+) = 273 [$M + H$] $^+$.

Preparation 7: 5-Chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid ethyl ester



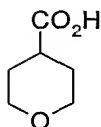
3-(2-Chloro-5-nitropyridin-4-yl)-2-oxopropionic acid ethyl ester (Preparation 6, 3.0g, 11.0mmol) was dissolved in ethanol (100mL) and THF (50mL). Iron powder (3.7g, 66.0mmol) and saturated ammonium chloride solution (50mL) were added and the mixture was heated under reflux for 2h. The mixture was cooled, filtered through celite and washed several times with ethyl acetate. The organic layers were combined, washed with brine (100mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound. δ_H (CD_3OD): 1.42 (3H, t), 4.44 (2H, q), 7.15 (1H, s), 7.70 (1H, s), 8.59 (1H, s); m/z (ES^+) = 225 [$M + H$] $^+$.

Preparation 8: 5-Chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid



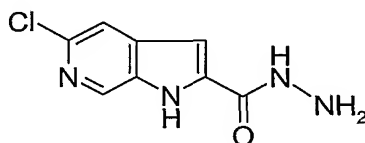
To a solution of 5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid ethyl ester (Preparation 7, 1.78g, 7.9mmol) in ethanol (70mL) was added sodium hydroxide solution (5.2mL, 2M, 10.3mmol) and the mixture was heated under reflux for 2h. The solvent was removed *in vacuo* and the solid dissolved in water (150mL) and acidified to pH 4 with acetic acid to give the title compound as a solid that was isolated by filtration. δ_H (CD_3OD): 7.13 (1H, s), 7.68 (1H, s), 8.58 (1H, s); m/z (ES^+) = 197 [$M + H$] $^+$.

Preparation 9: Tetrahydropyran-4-carboxylic acid



This compound was prepared by hydrolysis of the methyl ester according to the method of Spiegler and Goetz, *Ger. Offen.* (1987) DE 3536956 A1.

Preparation 10: 5-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide



Route 1

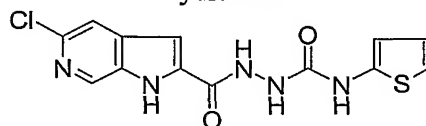
N'-(*tert*-Butyloxycarbonyl)-5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide (EXAMPLE 25, 930mg, 2.99mmol) was suspended in a mixture of dichloromethane and trifluoroacetic acid (1:1, 20mL). After 2h the mixture was concentrated *in vacuo* and the oily residue was dissolved in water (200mL). The aqueous layer was washed with ethyl acetate (2 x 50mL) and concentrated *in vacuo* to give the title compound as its trifluoroacetic acid salt. δ_{H} (d_6 DMSO) 7.36 (1H, s), 7.83 (1H, s), 8.66 (1H, s), 9.3-10.8 (3H, br s), 11.8-12.2 (1H, br s), 12.6 (1H, s); m/z (ES^+) = 211 [$M + \text{H}$] $^+$; RT = 0.42min.

Route 2

To a solution of 5-chloro-1*H*-pyrrolo [2,3-*c*] pyridine-2-carboxylic acid ethyl ester (Preparation 7, 880mg, 3.91mmol) in ethanol (30mL) was added hydrazine monohydrate (4.0mL, 78.22mmol). The resulting solution was refluxed at 90°C for 5h. The reaction mixture was cooled to rt and the precipitate was filtered and dried to give the title compound. m/z (ES^+) = 211 [$M + \text{H}$] $^+$; RT = 1.65min.

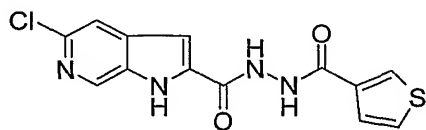
EXAMPLE 1

5-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid *N'*-(thiophene-2-yl-aminocarbonyl) hydrazide



DIPEA (53 μ L, 0.31mmol) and thienyl isocyanate (40 μ L, 0.32mmol) were added to a suspension of 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide trifluoroacetic acid salt (Preparation 10 – route 1, 101mg, 0.31mmol) in a mixture of toluene and 1,4-dioxane (10mL, 1:1). After stirring the mixture at 100°C for 12h, the reaction was allowed to cool to rt and the solvent was removed. The remaining oily residue was purified by flash chromatography on silica gel (toluene/acetone : 2/1) to give the title compound. δ_{H} (CDCl_3): 6.60 (1H, d), 6.78 (1H, m), 6.84 (1H, d), 7.26 (1H, d), 7.82 (1H, s), 8.61 (2H, m), 9.97 (1H, s); m/z (ES^+) = 336 [$M + \text{H}$] $^+$; RT = 2.97min.

EXAMPLE 2

Thiophene-3-carboxylic acid *N'*-(5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carbonyl)hydrazide

To a solution of 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide trifluoroacetic acid salt (Preparation 10 – route 1, 0.110g, 0.34mmol) in DMF (3mL) was added DIPEA (170.0μL, 1.02mmol). To the stirred solution, HOBt (0.046g, 0.34mmol), EDCI (0.078g, 0.41mmol), DIPEA (120.0μL, 0.68mmol) and thiophene-3-carboxylic acid (0.044g, 0.34mmol) were added. The reaction mixture was stirred at rt for 16h and then concentrated *in vacuo* to give an oil. On addition of ethyl acetate to the oil, a solid precipitated. The solid was filtered and dried to give the title compound. m/z (ES^+) = 321 [$M + H$] $^+$; RT = 2.84min.

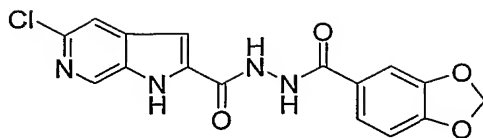
The coupling of the appropriate carboxylic acid with 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide, outlined in EXAMPLE 2, was also employed to prepare the compounds listed in Table 1 below.

Table 1

EX.	Structure	Name	RT	m/z (ES^+)
3		Furan-3-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.75	305
4		Tetrahydrofuran-3-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.59	309
5		1 <i>H</i> -Pyrrole-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.77	304
6		Benzoic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	3.02	315

EXAMPLE 7

Benzo[1,3]dioxole-5-carboxylic acid *N'*-(5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carbonyl)hydrazide

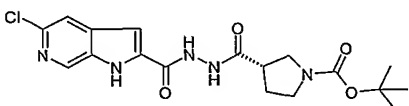
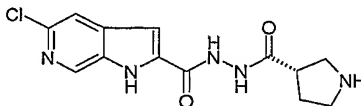


To a solution of 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide (Preparation 10 – route 2, 0.100g, 0.48mmol) in DMF (4mL) was added HOBt (0.064g, 0.48mmol), EDCI (0.110g, 0.58mmol), DIPEA (200μL, 0.96mmol) and piperonylic acid (0.079g, 0.48mmol). The reaction mixture was stirred at rt for 16h. The reaction mixture was poured into water (75mL) and extracted with ethyl acetate (2 x 150mL). The combined organic extract was washed with saturated sodium chloride (75mL), dried (MgSO₄) and concentrated *in vacuo* to give a solid. The solid obtained was purified by recrystallisation from methanol to give the title compound. *m/z* (ES⁺) = 359 [*M* + H]⁺; RT = 2.92min.

The coupling of the appropriate carboxylic acid with 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide, outlined above in EXAMPLE 7 was also employed to prepare the compounds listed in Table 2 below.

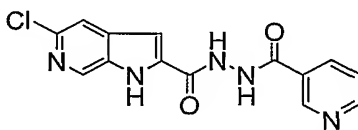
Table 2

EX.	Structure	Name	RT	<i>m/z</i> (ES ⁺)
8		Tetrahydropyran-4-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>]pyridine-2-carbonyl) hydrazide	2.49	323
9		Cyclopropane carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.42	279
10		4-Methylbenzoic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>]pyridine-2-carbonyl) hydrazide	2.95	329
11		2(<i>S</i>)-[<i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>] pyridine-2-carbonyl)-hydrazinocarbonyl] pyrrolidine-1-carboxylic acid tert-butyl ester	3.01	408
12		Pyrrolidine-2(<i>S</i>)-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	0.65	308

EX.	Structure	Name	RT	m/z (ES ⁺)
13		3(S)- <i>N'</i> -(5-Chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>] pyridine-2-carbonyl)-hydrazinocarbonyl] pyrrolidine-1-carboxylic acid tert-butyl ester	3.32	408
14		Pyrrolidine-3(<i>S</i>)-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.27	308

EXAMPLE 15

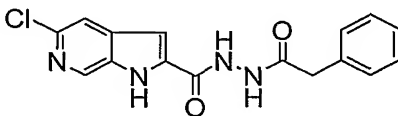
Pyridine-3-carboxylic acid *N'*-(5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carbonyl)hydrazide



To a solution of nicotinic acid hydrazide (35mg, 0.25mmol) in DMF (5mL) was added triethylamine (88μL, 0.64mmol), 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid (Preparation 8, 50mg, 0.25mmol), HOBT (34mg, 0.25mmol) and EDCI (50mg, 0.28mmol). The mixture was allowed to stir at rt for 16h. The solvent was removed *in vacuo* and the residue was partitioned between water (100mL) and ethyl acetate (100mL). The organic layer was dried (MgSO₄) and concentrated *in vacuo* to give an oil, which was purified by flash chromatography on silica gel (dichloromethane/methanol, 9/1) to give the title compound. m/z (ES⁺) = 316 [*M* + H]⁺; RT = 2.62min.

EXAMPLE 16

5-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid *N'*-phenylacetylhydrazide



To a solution of 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid (Preparation 8, 50mg, 0.25mmol) in DMF (10mL) was added DIPEA (89μL, 0.51mmol), HOBT (34mg, 0.25mmol), EDCI (63mg, 0.33mmol) and phenylacetic acid hydrazide (38mg, 0.25mmol) and the mixture was stirred at rt for 72h. The reaction mixture was partitioned between water (50mL) and ethyl acetate (3 x 30mL). The combined organics were washed with brine (20mL), dried (MgSO₄) and concentrated *in vacuo*. The crude material was chromatographed on silica gel eluting with methanol / dichloromethane (1:19) to give the title compound. m/z (ES⁺) = 329 [*M* + H]⁺; RT = 3.07min.

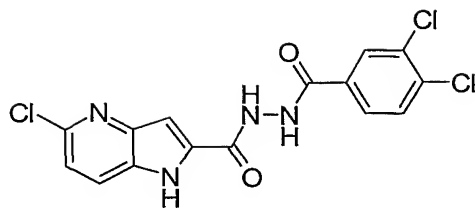
The coupling of the appropriate hydrazide with 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid, outlined in EXAMPLE 16, was also employed to prepare the compounds listed in Table 3 below.

Table 3

EX.	Structure	Name	RT (min)	m/z (ES ⁺)
17		5-Chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carboxylic acid <i>N'</i> -(4-chlorophenylaminocarbonyl)hydrazide	3.30	364
18		3,4-Dichlorobenzoic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	3.40	385
19		2,3-Dihydrobenzo[1,4]dioxine-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.95	329
20		2-Chlorophenoxy acetyl <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	3.30	379
21		Thiophene-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.95	321
22		Furan-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.88	305
23		1-Methyl-1 <i>H</i> -pyrrole-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	3.05	318

EXAMPLE 24

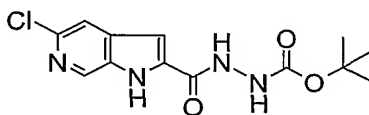
3,4-Dichlorobenzoic acid *N'*-(5-chloro-1*H*-pyrrolo[3,2-*b*]pyridine-2-carbonyl)hydrazide



To a solution of 5-chloro-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylic acid (Preparation 5, 20.0mg, 0.10mmol) in DMF (5mL) was added 3,4-dichlorobenzoic acid hydrazide (23mg, 0.11mmol), DIPEA (19.5μL, 0.11mmol) and HOBt (14.0mg, 0.10mmol). The resulting solution was stirred for 5min prior to the addition of EDCI (23mg, 1.20mmol). The reaction mixture was stirred for 16hr at rt then partitioned between water (10mL) and dichloromethane (20mL) on a hydrophobic frit. The aqueous phase was extracted with a further portion of dichloromethane (30mL) and the combined organics were concentrated *in vacuo*. Trituration of the resulting residue with ethyl acetate / dichloromethane gave the title compound. δ_H (d_6 DMSO): 12.25 (1H, s), 10.83 (2H, d), 8.17 (1H, s), 7.55 – 7.97 (3H, m), 7.38 (1H, s), 7.26 (1H, d); m/z (ES^+) = 383 [$M + H$] $^+$; RT = 3.37min.

EXAMPLE 25

5-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid *N'*-(*tert*butyloxycarbonyl)hydrazide



To a solution of 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid (Preparation 8, 2.05g, 10.4mmol) in DMF (30mL), *tert*-butyl carbazate (1.38g, 10.4mmol), DIPEA (3.5mL, 20.4mmol), HOBt (1.58g, 10.3mmol) and EDCI (2.54g, 13.3mmol) were added successively. The resulting solution was stirred for 12h at rt before adding water and brine (1:1, 200mL). The solution was extracted with ethyl acetate (4 x 50mL) and the combined organic layers were washed with dilute hydrochloric acid (1N, 50mL), dilute sodium hydroxide solution (1N, 50mL) and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a solid residue, which was purified by flash chromatography on silica gel (hexane/ethyl acetate, 1: 3) to give the title compound. δ_H ($CDCl_3$): 1.42 (9H, s), 7.19 (1H, s), 7.78 (1H, s), 8.60 (1H, s), 9.28 (1H, br s).

The biological activity of the compounds of the invention may be tested in the following assay systems:

In vitro GP activity

Materials:

α -D-Glucose-1-Phosphate (disodium salt), Glycogen, D-Glucose, Malachite Green Hydrochloride, Ammonium Molybdate tetrahydrate, BSA, HEPES and rabbit muscle phosphorylase *a* (P1261) were purchased from Sigma. All other reagents were analytical grade.

Method

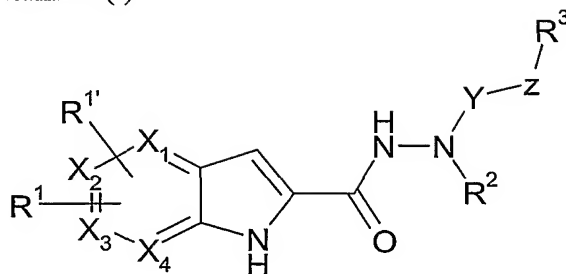
Glycogen phosphorylase assay *in vitro*:

An assay for glycogen phosphorylase activity in the reverse direction was developed based on the method described by Engers *et al.*, *Can. J. Biochem.*, 1970, 48, 746-754]. Rabbit muscle glycogen phosphorylase α (Sigma) was reconstituted at a stock concentration of 100 $\mu\text{g/mL}$ in 25mM Tris/HCl. The pH was measured in a 96-well plate in a final volume of 100 μL containing 50mM Hepes pH 7.2, 7.5mM glucose, 0.5mM glucose-1-phosphate and 1mg/mL glycogen. After incubation at 30°C for 30min, the inorganic phosphate released from glucose-1-phosphate was measured by the addition of 150 μL of malachite green/molybdate solution prepared as follows: 5mL of 4.2% ammonium molybdate in 4N HCl, 15mL of 0.045% malachite green, 50 μL of Tween 20. Following a 30min incubation at rt, the absorbance was measured at 620nm. For IC_{50} determination, 10 μL of a serial dilution of compound (100 μM to 0.004 μM) in DMSO was added to each reaction in duplicate with the equivalent concentration of DMSO added to the control uninhibited reaction. Dose response curves were then obtained by plotting % inhibition versus \log_{10} compound concentration. IC_{50} is defined as the concentration of compound achieving 50% inhibition under the assay conditions described.

Examples of compounds of the present invention demonstrated efficacy in the above assay with IC_{50} results in the range of better than 100 μM .

CLAIMS:

1. A compound of formula (I):



I

or a pharmaceutically acceptable salt thereof, wherein:

one of X_1 , X_2 , X_3 and X_4 is N and the others are C;

Y is $-C(O)-$, $-S(O)_2-$, or $-C(NH)-$;

Z is C_{1-4} alkylene, oxygen, $-(CH_2)_mO-$, $-O(CH_2)_m-$, $-NR-$, $-(CH_2)_mNR-$, $-NR(CH_2)_m-$, $-(CH_2)_mS(O)_2-$, or a bond;

m is 1, 2, 3, or 4;

R is C_{0-4} alkyl, C_{0-4} alkylaryl, or C_{0-4} alkylhetaryl;

R^1 and $R^{1'}$ are each independently, halogen, hydroxy, cyano, C_{0-4} alkyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, or ethynyl;

R^2 is C_{0-4} alkyl, $COOR^6$, COR^6 , C_{1-4} alkoxy C_{1-4} alkyl-, hydroxy C_{1-4} alkyl-, cycloalkyl C_{0-4} alkyl-, aryl C_{0-4} alkyl-, or hetaryl C_{0-4} alkyl-, wherein any of the aryl or hetaryl rings are optionally substituted with 1-2 independent halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-SO_2C_{1-4}alkyl$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents;

R^3 is hydrogen, $-COOC_{0-4}alkyl$, C_{1-4} alkoxy, C_{1-4} alkyl, aryl $C_{1-4}alkylthio-$, $-C_{0-4}alkylaryl$, $-C_{0-4}alkylhetaryl$, $-C_{0-4}alkylcycloalkyl$, or $-C_{0-4}alkylheterocyclyl$, wherein any of the rings is optionally substituted with 1-3 independent halogen, cyano, C_{1-4} alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, $-C_{0-4}alkylNHC(O)O(C_{1-4}alkyl)$, $-C_{0-4}alkylNR^7R^8$, $-C(O)R^9$, $C_{1-4}alkoxyC_{0-4}alkyl-$, $-COOC_{0-4}alkyl$, $-C_{0-4}alkylNHC(O)R^9$, $-C_{0-4}alkylC(O)N(R^{10})_2$, $-C_{1-4}alkoxyC_{1-4}alkoxy$, hydroxy $C_{0-4}alkyl-$, $-NHSO_2R^{10}$, $-SO_2(C_{1-4}alkyl)$, $-SO_2NR^{11}R^{12}$, 5- to 6-membered heterocyclyl, phenyl $C_{0-2}alkoxy$, or phenyl $C_{0-2}alkyl$ substituents, wherein phenyl is optionally substituted with 1-2 independent halogen, cyano, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-SO_2C_{1-4}alkyl$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents, or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo ($=O$) substituent;

or R^3 is $-NR^4(-C_{0-4}alkylR^5)$;

R^4 is $C_{0-3}alkyl$, $-C_{2-3}alkyl-NR^7R^8$, $C_{3-6}cycloalkyl$ optionally substituted by hydroxy $C_{0-4}alkyl-$ further optionally substituted by hydroxy, $C_{1-2}alkoxyC_{2-4}alkyl-$, or $C_{1-2}alkyl-S(O)_n-C_{2-3}alkyl-$;

n is 0, 1, or 2;

R^5 is hydrogen, hydroxy $C_{2-3}alkyl-$, $C_{1-2}alkoxyC_{0-4}alkyl-$, or aryl, hetaryl, or heterocyclyl;

wherein a heterocyclic nitrogen-containing R⁵ ring optionally is mono-substituted on the ring nitrogen with C₁₋₄alkyl, benzyl, benzoyl, C₁₋₄alkyl-C(O)-, -SO₂C₁₋₄alkyl, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), C₁₋₄alkoxycarbonyl, or aryl(C₁₋₄alkoxy)carbonyl; and wherein the R⁵ rings are optionally mono-substituted on a ring carbon with halogen, cyano, C₁₋₄alkyl-C(O)-, C₁₋₄alkyl-SO₂-, C₁₋₄alkyl, C₁₋₄alkoxy, hydroxy, -N(C₀₋₄alkyl)(C₀₋₄alkyl), hydroxyc₀₋₄alkyl-, or C₀₋₄alkylcarbonyl-, provided that no quaternised nitrogen is included; or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo (=O) substituent;

R⁶ is C₁₋₄alkyl, aryl, or hetaryl;

R⁷ and R⁸ are independently C₀₋₄alkyl, C₃₋₆cycloalkyl, or CO(C₁₋₄alkyl);

R⁹ is C₁₋₄alkyl, or C₃₋₆cycloalkyl;

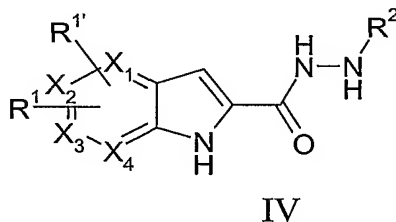
R¹⁰ is C₀₋₄alkyl, or C₃₋₆cycloalkyl; and

R¹¹ and R¹² are independently C₀₋₄alkyl or together with the nitrogen to which they are attached may form a 4- to 6-membered heterocycle;

provided there are no nitrogen-oxygen, nitrogen-nitrogen, oxygen-oxygen or nitrogen-halogen bonds in the grouping -Y-Z-R³.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X₃ is N.
3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X₁ is N.
4. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Y is -C(O)- or -S(O)₂-.
5. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Z is C₁₋₄alkylene, oxygen, -(CH₂)_mO-, -NR- or a bond.
6. A compound according to any one of the preceding claims 1, or a pharmaceutically acceptable salt thereof, wherein R¹ and R^{1'} are each independently, hydrogen or halogen.
7. A compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein one of R¹ and R^{1'} is hydrogen and the other is 5-chloro.
8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R² is hydrogen.
9. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen, -NR⁴R⁵, -NR⁴(-C₁₋₄alkylR⁵), aryl, hetaryl, or heterocyclyl wherein any of the rings is optionally substituted as defined in claim 1.
10. A compound of formula (I) as defined in any one of Examples 1 to 25, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
12. A method for the treatment of a disease or condition in which glycogen phosphorylase plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
13. A method for the treatment of hyperglycemia or diabetes comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
14. A method for the prevention of diabetes in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering to a subject in need thereof an effective prophylactic amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
15. A method for the treatment of hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, or achieving cardioprotection or inhibition of abnormal cell growth, comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
16. A compound of formula (IV):



wherein R¹, R^{1'}, R², X₁, X₂, X₃ and X₄ are as defined in claim 1, or a protected derivative thereof.

1/11

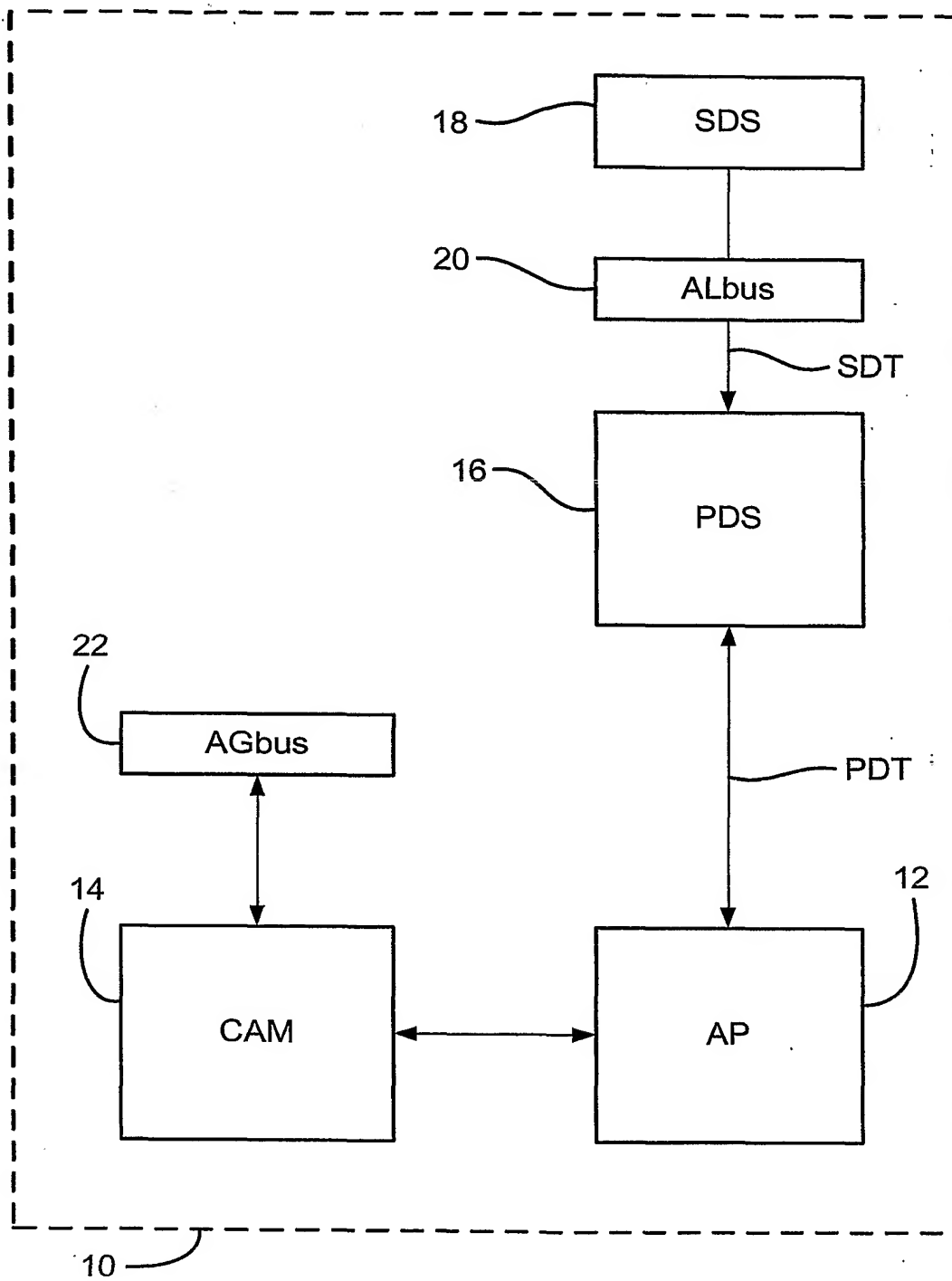
**Fig.1**

Fig.2

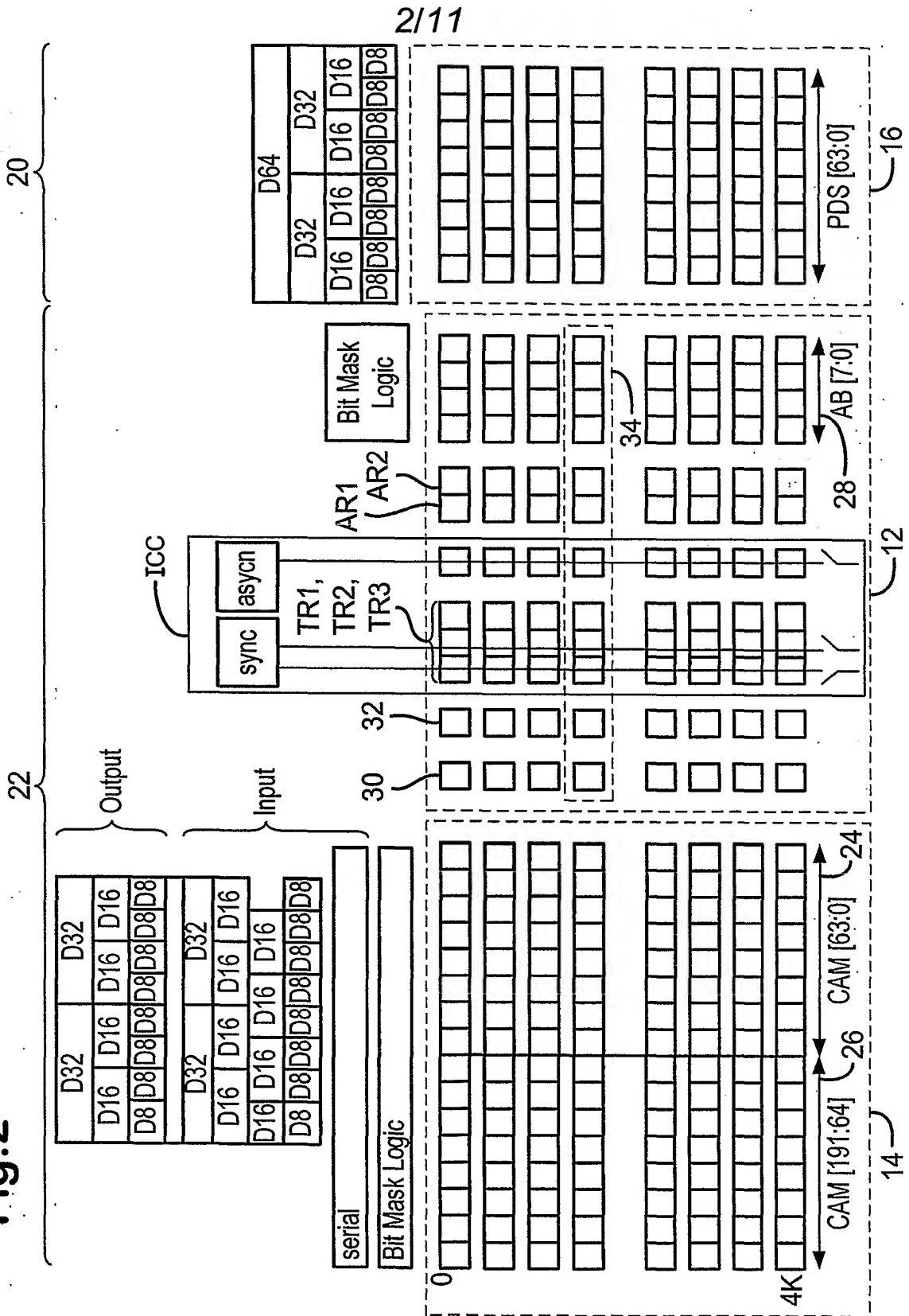
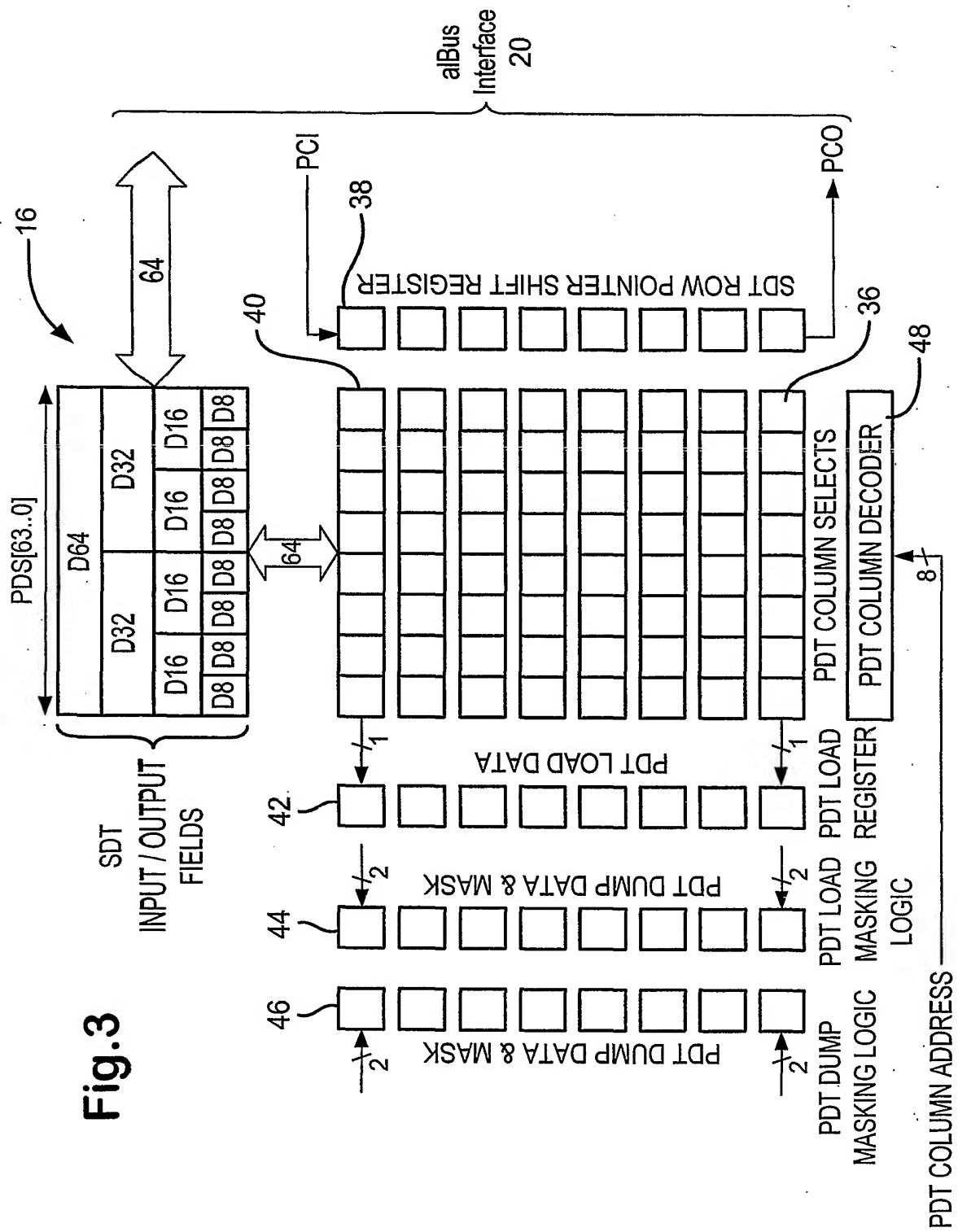
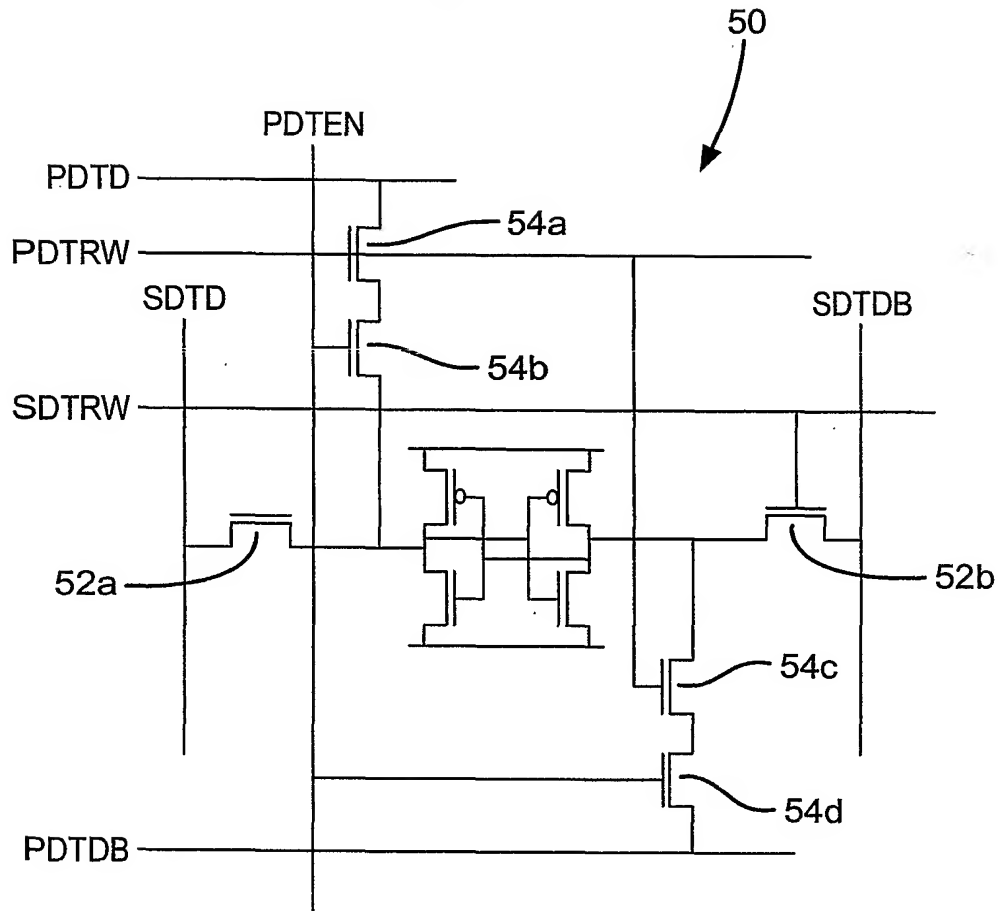


Fig. 3



4/11

Fig.4

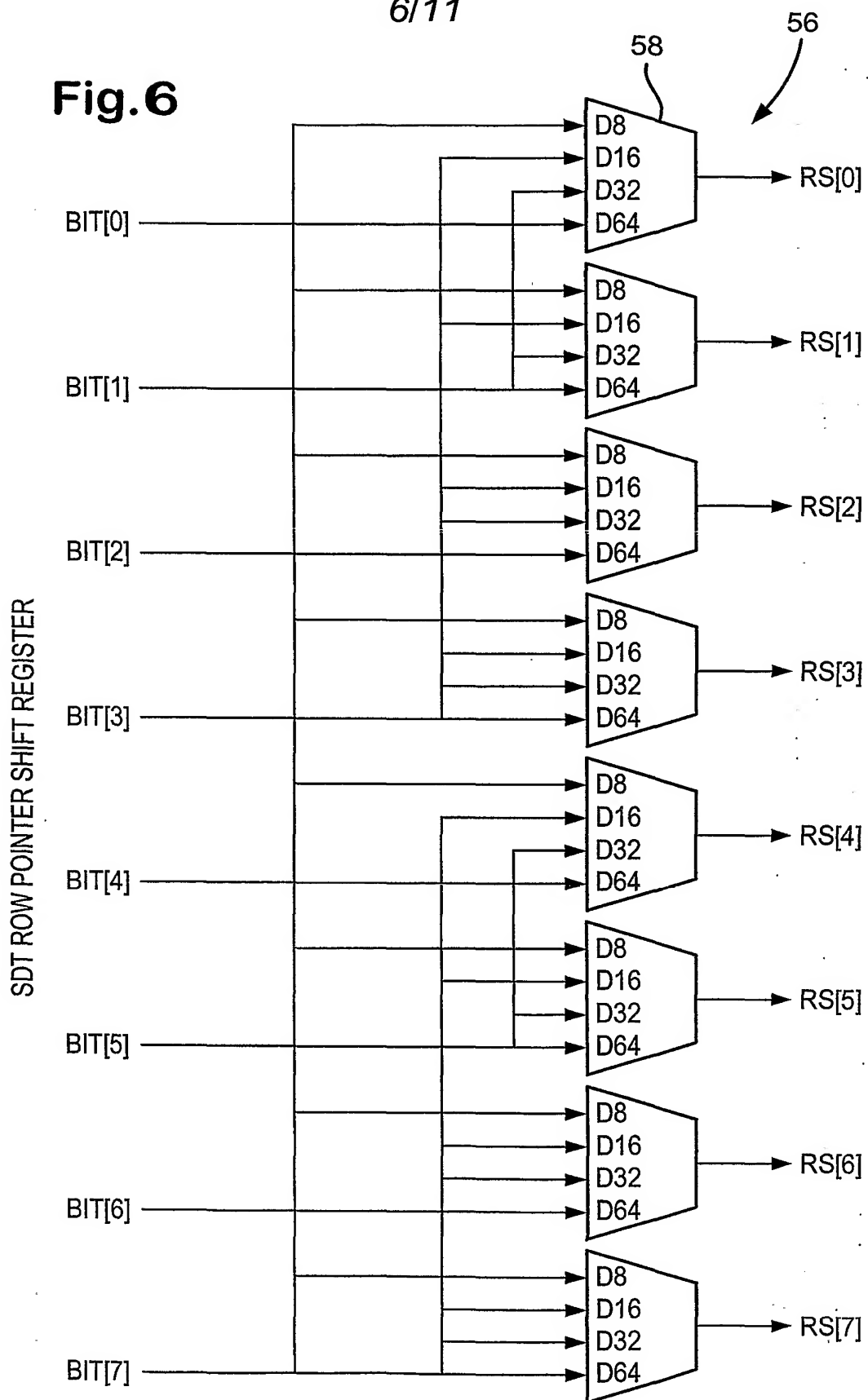
5/11

Fig.5

row address MOD 8	Row Strobe logic conditions
0	$SDTRW_A[0] = RS[0]$
	$SDTRW_B[0] = \sim D8.RS[0]$
	$SDTRW_C[0] = (D32+D64).RS[0]$
	$SDTRW_D[0] = D64.RS[0]$
1	$SDTRW_A[1] = (D8+D64).RS[1]$
	$SDTRW_B[1] = (D16+D64).RS[1]$
	$SDTRW_C[1] = (D32+D64).RS[1]$
	$SDTRW_D[1] = D64.RS[1]$
2	$SDTRW_A[2] = \sim D16.RS[2]$
	$SDTRW_B[2] = (D16+D64).RS[2]$
	$SDTRW_C[2] = (D32+D64).RS[2]$
	$SDTRW_D[2] = D64.RS[2]$
3	$SDTRW_A[3] = (D8+D64).RS[3]$
	$SDTRW_B[3] = \sim D8.RS[3]$
	$SDTRW_C[3] = (D32+D64).RS[3]$
	$SDTRW_D[3] = D64.RS[3]$
4	$SDTRW_A[4] = (D8+D64).RS[4]$
	$SDTRW_B[4] = \sim D8.RS[4]$
	$SDTRW_C[4] = (D32+D64).RS[4]$
	$SDTRW_D[4] = D64.RS[4]$
5	$SDTRW_A[5] = \sim D16.RS[5]$
	$SDTRW_B[5] = (D16+D64).RS[5]$
	$SDTRW_C[5] = (D32+D64).RS[5]$
	$SDTRW_D[5] = D64.RS[5]$
6	$SDTRW_A[6] = (D8+D64).RS[6]$
	$SDTRW_B[6] = (D16+D64).RS[6]$
	$SDTRW_C[6] = (D32+D64).RS[6]$
	$SDTRW_D[6] = D64.RS[6]$
7	$SDTRW_A[7] = RS[7]$
	$SDTRW_B[7] = \sim D8.RS[7]$
	$SDTRW_C[7] = (D32+D64).RS[7]$
	$SDTRW_D[7] = D64.RS[7]$

Table 2

6/11

Fig.6

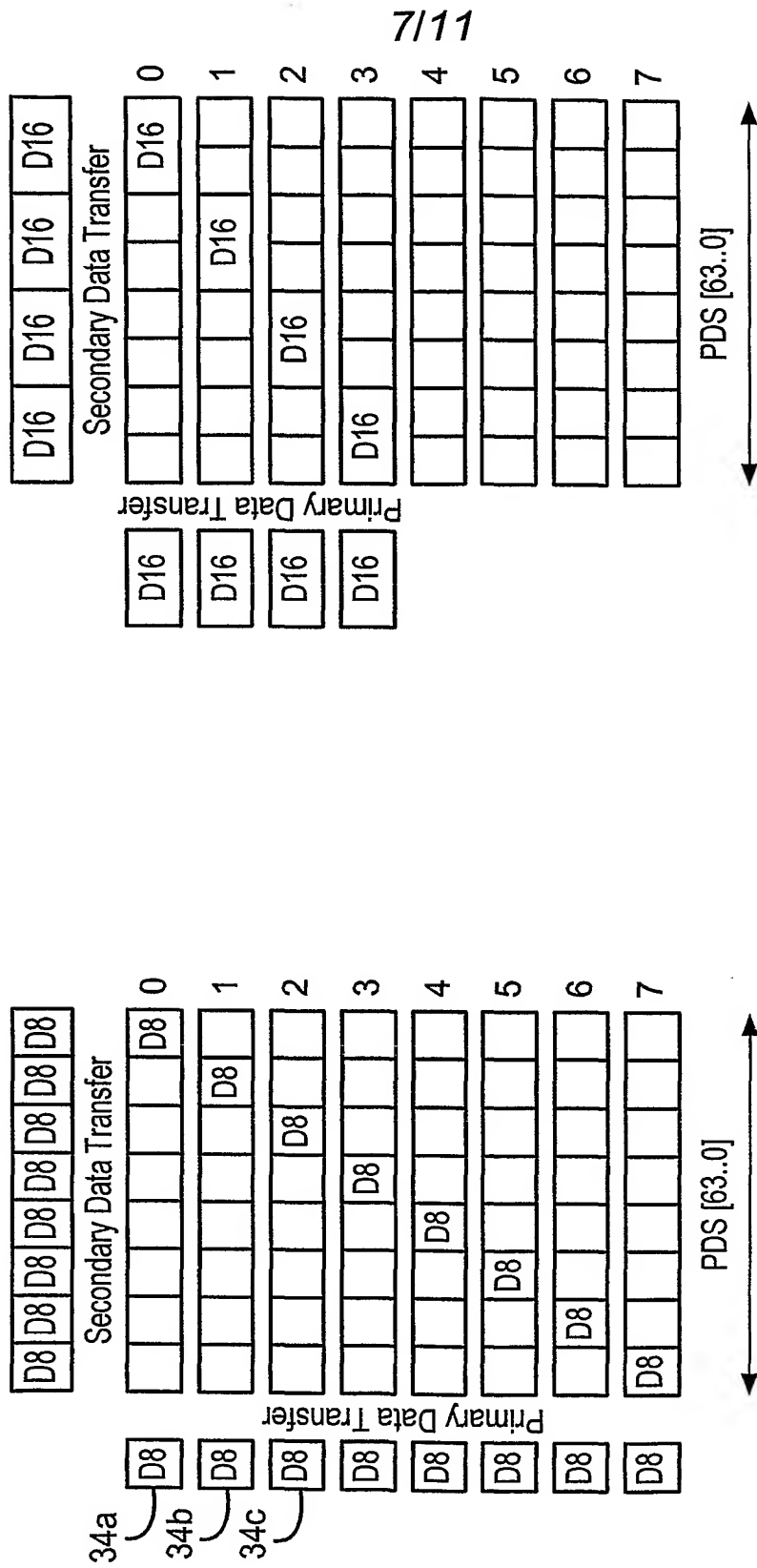


Fig.7 (b)

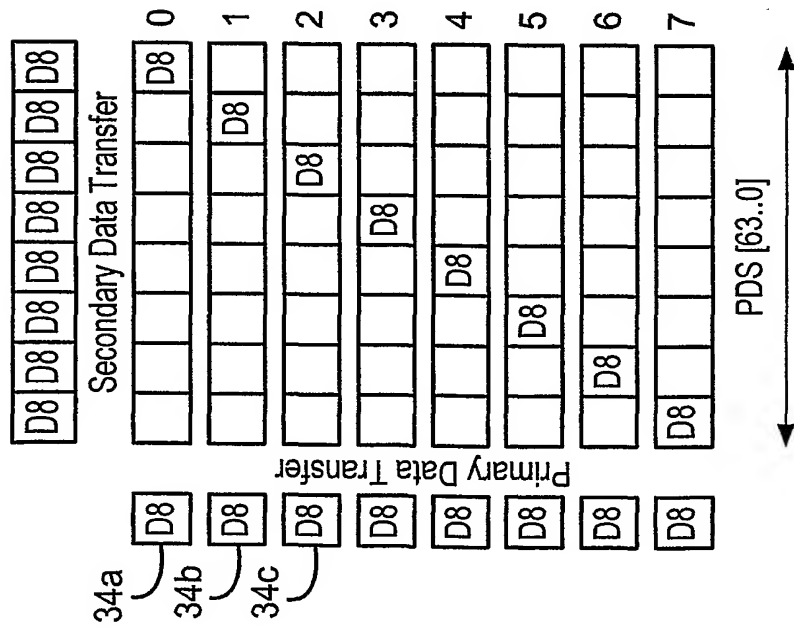


Fig.7 (a)

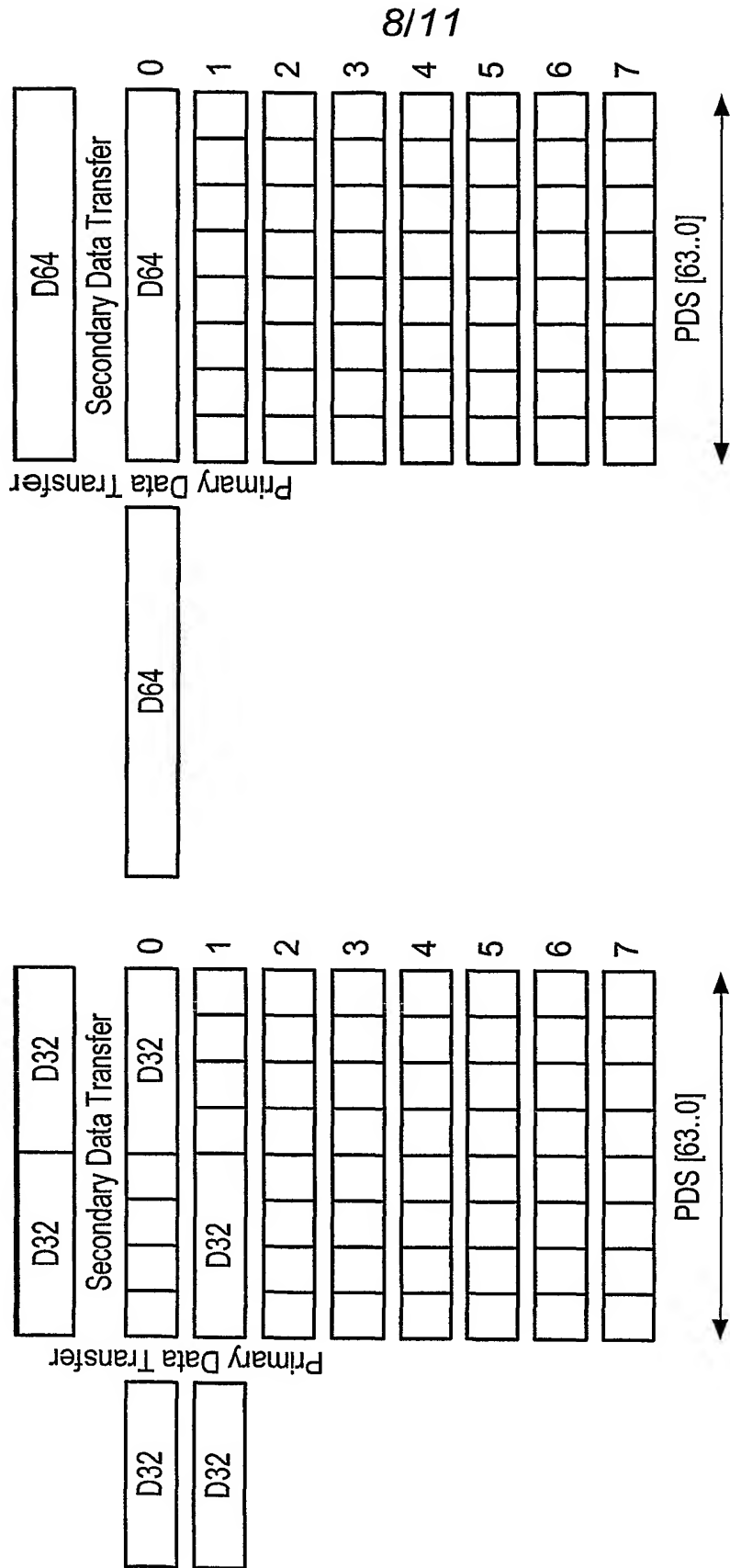


Fig. 7 (c)

Fig. 7 (d)

9/11
Fig.8

byte address	column address	Row Strobe logic conditions
0	7..0	$PDTEN_A[7..0] = BS[0].CS[7..0]$
		$PDTEN_B[7..0] = \sim D8.BS[0].CS[7..0]$
		$PDTEN_C[7..0] = (D32+D64).BS[0].CS[7..0]$
		$PDTEN_D[7..0] = D64.BS[0].CS[7..0]$
1	15..8	$PDTEN_A[15..8] = (D8+D64).BS[1].CS[15..8]$
		$PDTEN_B[15..8] = \sim D8.BS[1].CS[15..8]$
		$PDTEN_C[15..8] = (D32+D64).BS[1].CS[15..8]$
		$PDTEN_D[15..8] = D64.BS[1].CS[15..8]$
2	24..16	$PDTEN_A[24..16] = \sim D16.BS[2].CS[24..16]$
		$PDTEN_B[24..16] = (D16+D64).BS[2].CS[24..16]$
		$PDTEN_C[24..16] = (D32+D64).BS[2].CS[24..16]$
		$PDTEN_D[24..16] = D64.BS[2].CS[24..16]$
3	31..25	$PDTEN_A[31..25] = (D8+D64).BS[3].CS[31..25]$
		$PDTEN_B[31..25] = \sim D8.BS[3].CS[31..25]$
		$PDTEN_C[31..25] = (D32+D64).BS[3].CS[31..25]$
		$PDTEN_D[31..25] = D64.BS[3].CS[31..25]$
4	39..32	$PDTEN_A[31..25] = (D8+D64).BS[4].CS[39..32]$
		$PDTEN_B[31..25] = \sim D8.BS[4].CS[39..32]$
		$PDTEN_C[31..25] = (D32+D64).BS[4].CS[39..32]$
		$PDTEN_D[31..25] = D64.BS[4].CS[39..32]$
5	47..40	$PDTEN_A[24..16] = \sim D16.BS[5].CS[47..40]$
		$PDTEN_B[24..16] = (D16+D64).BS[5].CS[47..40]$
		$PDTEN_C[24..16] = (D32+D64).BS[5].CS[47..40]$
		$PDTEN_D[24..16] = D64.BS[5].CS[47..40]$
6	55..48	$PDTEN_A[15..8] = (D8+D64).BS[6].CS[55..48]$
		$PDTEN_B[15..8] = \sim D8.BS[6].CS[55..48]$
		$PDTEN_C[15..8] = (D32+D64).BS[6].CS[55..48]$
		$PDTEN_D[15..8] = D64.BS[6].CS[55..48]$
7	63..56	$PDTEN_A[7..0] = BS[7].CS[63..56]$
		$PDTEN_B[7..0] = \sim D8.BS[7].CS[63..56]$
		$PDTEN_C[7..0] = (D32+D64).BS[7].CS[63..56]$
		$PDTEN_D[7..0] = D64.BS[7].CS[63..56]$

Table 4

10/11

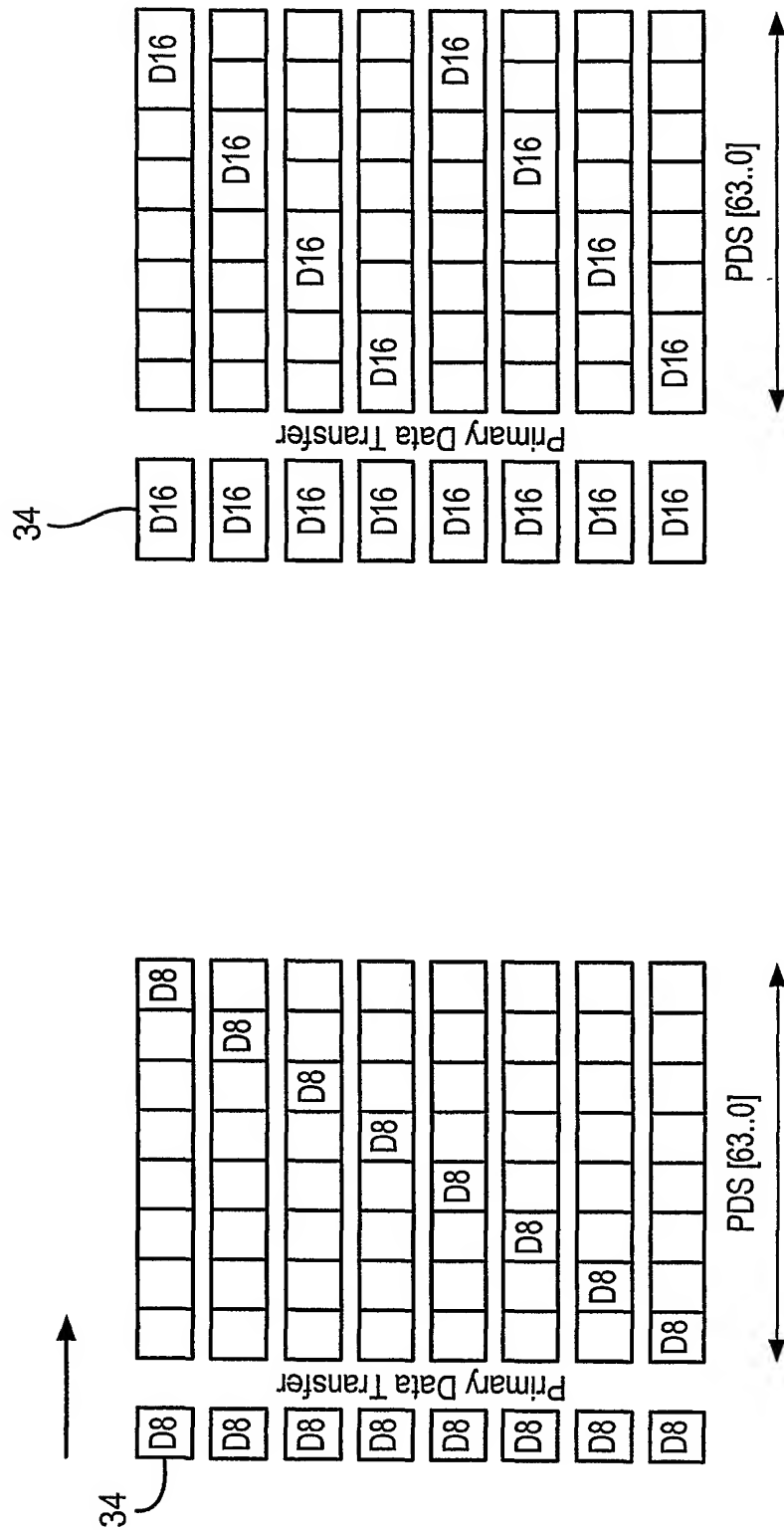


Fig.9 (b)

Fig.9 (a)

11/11

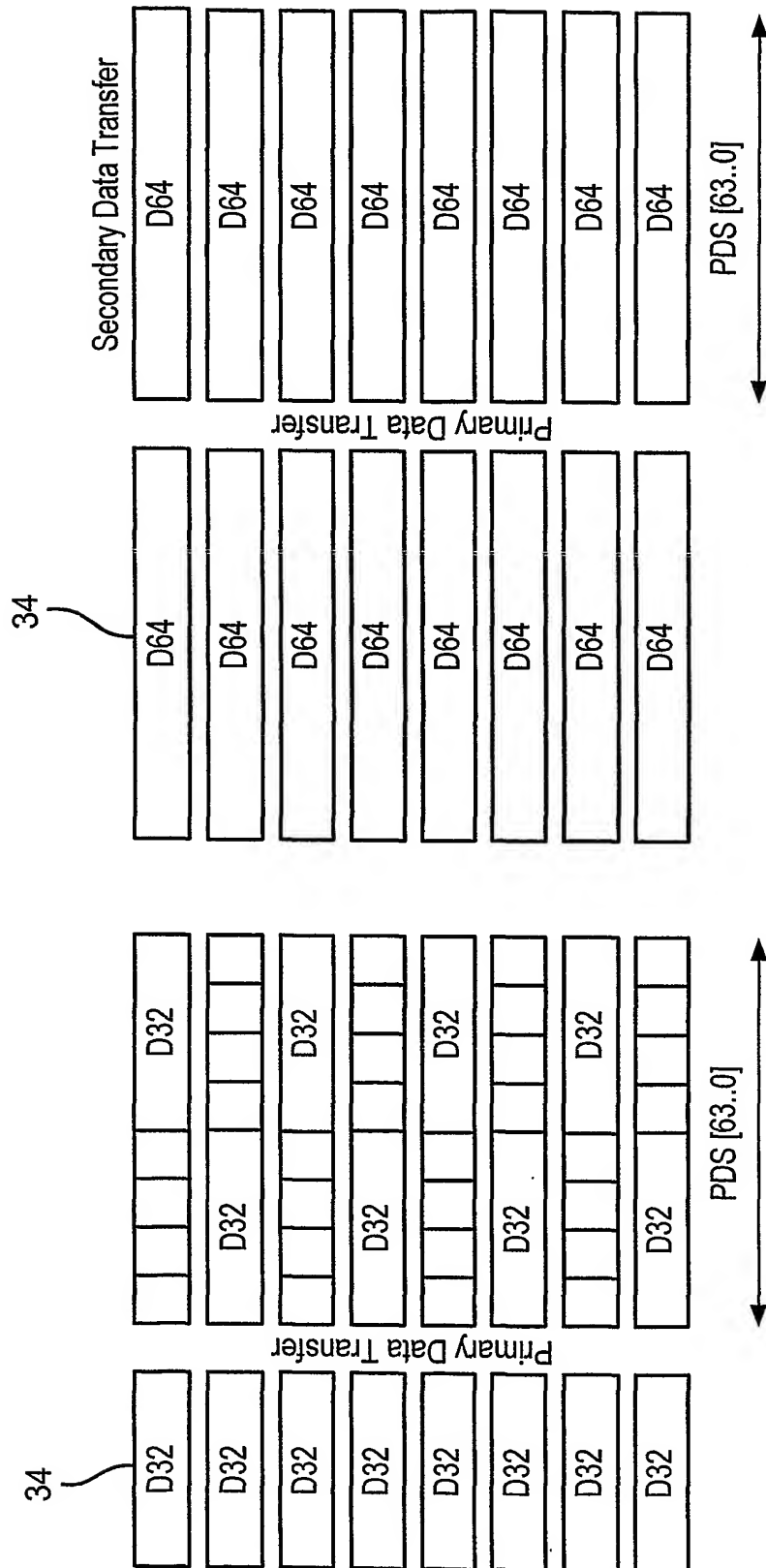


Fig.9 (d)

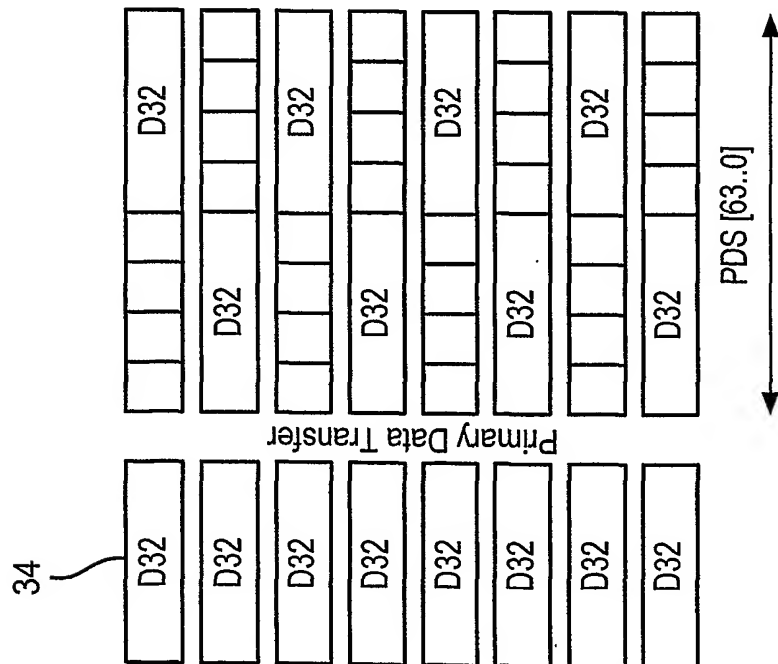


Fig.9 (c)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/000885

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 A61K31/437 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 2004/104001 A (OSI PHARMACEUTICALS, INC; BRADLEY, STUART, EDWARD; KRULLE, THOMAS, MAR) 2 December 2004 (2004-12-02) cited in the application abstract examples claims	1-16
Y	WO 03/037864 A (JAPAN TOBACCO INC; NAKAMURA, TAKESHI; TAKAGI, MASAKI; UEDA, NOBUHISA) 8 May 2003 (2003-05-08) cited in the application abstract examples claims	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

24 June 2005

Date of mailing of the international search report

01/07/2005

Name and mailing address of the ISA

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Fax (+31-70) 340-3016

Authorized officer

Stix-Malaun, E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/000885

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/GB2005/000885

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004104001 A	02-12-2004	WO 2004104001 A2	02-12-2004
WO 03037864 A	08-05-2003	CA 2465382 A1	08-05-2003
		EP 1452526 A1	01-09-2004
		WO 03037864 A1	08-05-2003
		JP 2003201279 A	18-07-2003
		US 2005054696 A1	10-03-2005

CORRECTED VERSION

(19) World Intellectual Property
Organization
International Bureau



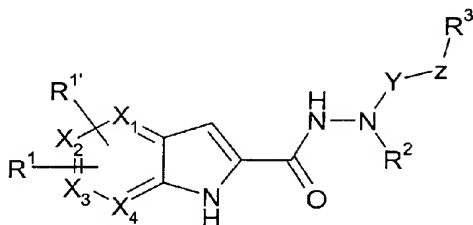
(43) International Publication Date
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(10) International Publication Number
WO 2005/085245 A1

- (51) International Patent Classification⁷: **C07D 471/04**,
A61K 31/437, A61P 3/00
- (21) International Application Number:
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- (22) International Filing Date: 8 March 2005 (08.03.2005)
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- (26) Publication Language: English
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60/551,254 8 March 2004 (08.03.2004) US
- (71) Applicant (for all designated States except US): **PROSIDION LIMITED** [GB/GB]; Watlington Road, Oxford, Oxfordshire OX4 6LT (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **BRADLEY, Stuart, Edward** [GB/GB]; Prosidion Limited, Watlington Road, Oxford, Oxfordshire OX4 6LT (GB). **JEEVARATNAM, Revathy, Perpetua** [LK/GB]; Prosidion Limited, Watlington Road, Oxford, Oxfordshire OX4 6LT (GB). **KRULLE, Thomas, Martin** [DE/GB]; Prosidion Limited, Watlington Road, Oxford, Oxfordshire OX4 6LT (GB). **PROCTER, Martin, James** [GB/GB]; Prosidion Limited, Watlington Road, Oxford, Oxfordshire OX4 6LT (GB). **ROWLEY, Robert, John** [GB/GB]; Prosidion Limited, Watlington Road, Oxford, Oxfordshire OX4 6LT (GB). **THOMAS, Gerard, Hugh** [GB/GB]; Prosidion Limited, Watlington Road, Oxford, Oxfordshire OX4 6LT (GB). **VALDES, Ana** [ES/GB]; Prosidion Limited, Watlington Road, Oxford, Oxfordshire OX4 6LT (GB).
- (74) Agent: **BLAKEY, Alison**; Prosidion Limited, Watlington Road, Oxford, Oxfordshire OX4 6LT (GB).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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see PCT Gazette No. 45/2005 of 10 November 2005, Section II
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRROLOPYRIDINE-2-CARBOXYLIC ACID HYDRAZIDES



(I)

(57) Abstract: Compounds of Formula (I) or pharmaceutically acceptable salts thereof, are inhibitors of glycogen phosphorylase and are useful in the prophylactic or therapeutic treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia e.g. myocardial ischemia, or as cardioprotectants or inhibitors of abnormal cell growth.



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(19) World Intellectual Property Organization
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15 September 2005 (15.09.2005)

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(10) International Publication Number
WO 2005/085245 A1(51) International Patent Classification⁷: **C07D 471/04**,
A61K 31/437, A61P 3/00(74) Agent: **BLAKEY, Alison**; Prosidion Limited, Watlington
Road, Oxford, Oxfordshire OX4 6LT (GB).(21) International Application Number:
PCT/GB2005/000885(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
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(30) Priority Data:
60/551,254 8 March 2004 (08.03.2004) US(71) Applicant (*for all designated States except US*): **PROSID-
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fordshire OX4 6LT (GB).

(72) Inventors; and

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Edward [GB/GB]; Prosidion Limited, Watlington Road,
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Revathy, Perpetua [LK/GB]; Prosidion Limited, Watling-
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Gerard, Hugh [GB/GB]; Prosidion Limited, Watlington
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Ana [ES/GB]; Prosidion Limited, Watlington Road,
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GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
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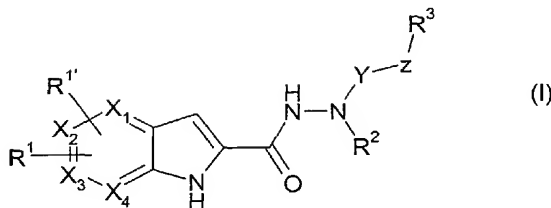
see PCT Gazette No. 01/2006 of 5 January 2006, Section II

Previous Correction:

see PCT Gazette No. 45/2005 of 10 November 2005, Sec-
tion II

[Continued on next page]

(54) Title: PYRROLOPYRIDINE-2-CARBOXYLIC ACID HYDRAZIDES



(57) Abstract: Compounds of Formula (I) or pharmaceutically acceptable salts thereof, are inhibitors of glycogen phosphorylase and are useful in the prophylactic or therapeutic treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia e.g. myocardial ischemia, or as cardioprotectants or inhibitors of abnormal cell growth.

WO 2005/085245 A1



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE OF THE INVENTION

PYRROLOPYRIDINE-2-CARBOXYLIC ACID HYDRAZIDES AS INHIBITORS OF GLYCOGEN PHOSPHORYLASE

BACKGROUND OF THE INVENTION

The present invention is directed to pyrrolopyridine-2-carboxylic acid hydrazides. In particular, the present invention is directed to pyrrolopyridine-2-carboxylic acid hydrazides that are inhibitors of glycogen phosphorylase.

Insulin dependent Type I diabetes and non-insulin dependent Type II diabetes continue to present treatment difficulties even though clinically accepted regimens that include diet, exercise, hypoglycemic agents, and insulin are available. Treatment is patient dependent therefore there is a continuing need for novel hypoglycemic agents, particularly ones that may be better tolerated with fewer adverse effects.

The liver and certain other organs produce glucose (thereby raising the blood sugar level) by breaking down glycogen or by synthesizing glucose from small molecule precursors. The breakdown of glycogen is catalyzed by glycogen phosphorylase enzyme. Accordingly, inhibiting glycogen phosphorylase ("GP") may lower the elevated blood sugar level in diabetic patients.

Similarly, hypertension and its associated pathologies such as, for example, atherosclerosis, lipidemia, hyperlipidemia and hypercholesterolemia have been associated with elevated insulin levels (hyperinsulinemia), which can lead to abnormal blood sugar levels. Furthermore, myocardial ischemia can result. Such maladies may be treated with hypoglycemic agents, including compounds that inhibit glycogen phosphorylase. Accordingly, it is accepted that compounds that inhibit glycogen phosphorylase (see, for example, U.S. Patent No. 6,297,269) are useful in the treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, atherosclerosis or myocardial ischemia. Nevertheless, it would be desirable to obtain other novel compounds that inhibit glycogen phosphorylase.

R. Kurukulasuriya, J.T. Link, et al., *Current Medicinal Chem.*, 10:99-121(2003) describes "Prospects for Pharmacologic Inhibition of Hepatic Glucose Production." R. Kurukulasuriya, J.T. Link, et al., *Current Medicinal Chem.*, 10:123-153(2003) describes "Potential Drug Targets and Progress Towards Pharmacologic Inhibition of Hepatic Glucose Production."

U.S. Patent No. 6,297,269 and European Patent No. EP 0832066 describes substituted *N*-(indole-2-carbonyl)amides and derivatives as glycogen phosphorylase inhibitors. U.S. Patent Nos. 6,107,329 and 6,277,877 describe substituted *N*-(indole-2-carbonyl)glycinamides and derivatives as glycogen phosphorylase inhibitors. U.S. Patent No. 6,399,601 describes bicyclic pyrrolyl amides as glycogen phosphorylase inhibitors. International Patent Publication No. WO 03/037864 describes indole derivatives as glycogen phosphorylase inhibitors. European Patent Application Nos. EP 0978276 and EP 1136071 describe inhibitors of human glycogen phosphorylase and their use. International Patent Publication No. WO 01/68055 describes glycogen phosphorylase inhibitors. U.S. Patent No. 5,952,322 describes a method of reducing non-cardiac ischemial tissue damage using glycogen phosphorylase inhibitors.

European Patent Application No. EP1177791 describes the use of glycogen phosphorylase inhibitors to inhibit abnormal cell growth, e.g. in the treatment of cancer and hyperproliferative disorders.

International Patent Publication No. WO 04/104001 (published after the priority date of the present application) discloses pyrrolopyridine-2-carboxylic acid amide inhibitors of glycogen phosphorylase.

International Patent Publication No. WO 04/113345 (published after the priority date of the present application) discloses fused pyrrole compounds as inhibitors of glycogen phosphorylase.

International Patent Publication No. WO 01/55146 describes arylamidines. International Patent Publication No. WO 01/62775 describes antiarrhythmic peptides. International Patent Publication No. WO 01/96346 describes tricyclic compounds. International Patent Publication No. WO 02/16314 describes substituted polyamine compounds. International Patent Publication No. WO 02/20475 describes serine protease activity inhibitors. International Patent Publication No. WO 02/40469 describes bombesin receptor antagonists. International Patent Publication No. WO 02/46159 describes guanidine and amidine derivatives. International Patent Publication No. WO 00/69815 describes ureido-substituted cyclic amine derivatives.

International Patent Publication No. WO 00/43384 describes aromatic heterocyclic compounds. International Patent Publication Nos. WO 02/26697 and WO 00/76970 describe aromatic derivatives. International Patent Publication No. WO 01/32622 describes indoles. European Patent Application No. EP 1101759 describes phenylazole compounds. European Patent Application No. EP 1179341 describes cyclic amino compounds. U.S. Patent No. 6,037,325 describes substituted heterocyclic compounds. U.S. Patent No. 5,672,582 describes 4-substituted cyclohexylamine derivatives. European Patent Application No. EP 1201239 describes cyclic amine CCR3 antagonists. International Patent Publication No. WO 98/25617 describes substituted arylpiperazines. U.S. Patent No. 5,756,810 describes preparing 3-nitro benzoate compounds.

U.S. Patent No. 5,710,153 describes tetrazole compounds. U.S. Patent Nos. 6,174,887 and 6,420,561 describe amide compounds. S.P. Hiremath et al., *Acta Ciencia Indica*, XVIII:397(1992) describes the synthesis and biological activities of indolylthiosemicarbazides and semicarbazides. International Patent Publication No. WO 96/36595 describes 3,4-disubstituted phenylsulfonamides. U.S. Patent No. 5,618,825 describes combinatorial sulfonamide libraries. European Patent Application No. EP 0810221 describes oxygen-containing heterocyclic derivatives. European Patent Application No. 0345990 describes polypeptide compounds. European Patent Application No. 0254545 describes diamine compounds.

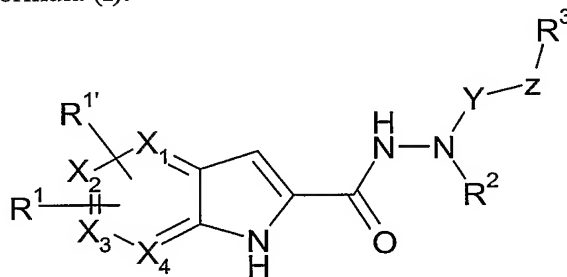
International Patent Publication No. WO 97/31016 describes inhibitors of SH2-mediated processes. U.S. Patent No. 6,034,067 describes serine protease inhibitors. International Patent Publication No. WO 97/17985 and U.S. Patent No. 6,107,309 describe hemoregulatory compounds. U.S. Patent No. 6,432,921 describes thrombin inhibitors. U.K. Patent Application No. GB 2292149 describes peptide inhibitors of pro-interleukin-1 β converting enzyme. U.S. Patent No. 5,821,241 describes fibrinogen receptor antagonists.

International Patent Publication No. WO 01/02424 describes peptide boronic acid compounds. U.S. Patent Nos. 6,001,811, 5,869,455 and 5,618,792 describe oxadiazole, thiadiazole and triazole peptoids. U.S. Patent Nos. 5,885,967, 6,090,787 and 6,124,277 describe thrombin inhibiting peptide derivatives. U.S. Patent No. 6,455,529 describes adhesion receptor antagonists. U.S. Patent No. 6,410,684 describes serine protease inhibitors.

International Patent Publication No. WO 01/94310 describes bis-heterocyclic alkaloids. U.S. Patent Publication No. 20030004162A1, European Patent Application No. EP 0846464 and International Patent Publication No. WO 96/39384 describe glycogen phosphorylase inhibitors. International Patent Publication No. WO 97/28798 describes pyrrolidine derivatives. U.S. Patent No. 5,346,907 describes amino acid analogs.

SUMMARY OF THE INVENTION

Compounds of formula (I):

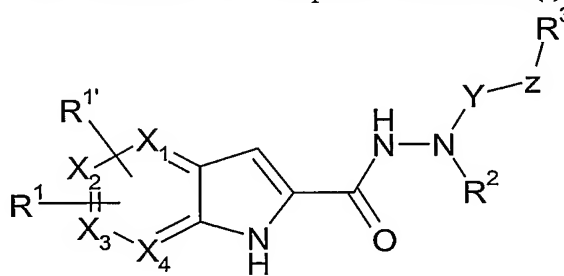


I

or pharmaceutically acceptable salts thereof, are inhibitors of glycogen phosphorylase and are useful in the prophylactic or therapeutic treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia e.g. myocardial ischemia, or as cardioprotectants or inhibitors of abnormal cell growth.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I):



I

or a pharmaceutically acceptable salt thereof, wherein:

one of X_1 , X_2 , X_3 and X_4 is N and the others are C;

Y is $-C(O)-$, $-S(O)_2-$, or $-C(NH)-$;

Z is C_{1-4} alkylene, oxygen, $-(CH_2)_mO-$, $-O(CH_2)_m-$, $-NR-$, $-(CH_2)_mNR-$, $-NR(CH_2)_m-$, $-(CH_2)_mS(O)_2-$, or a bond;

m is 1, 2, 3, or 4;

R is C_{0-4} alkyl, C_{0-4} alkylaryl, or C_{0-4} alkylhetaryl;

R^1 and $R^{1'}$ are each independently, halogen, hydroxy, cyano, C_{0-4} alkyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, or ethynyl;

R^2 is C_{0-4} alkyl, $COOR^6$, COR^6 , C_{1-4} alkoxy C_{1-4} alkyl-, hydroxy C_{1-4} alkyl-, cycloalkyl C_{0-4} alkyl-, aryl C_{0-4} alkyl-, or hetaryl C_{0-4} alkyl-, wherein any of the aryl or hetaryl rings are optionally substituted with 1-2 independent halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-SO_2C_{1-4}alkyl$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents;

R^3 is hydrogen, $-COOC_{0-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkyl$, aryl $C_{1-4}alkylthio$ -, $-C_{0-4}alkylaryl$, $-C_{0-4}alkylhetaryl$, $-C_{0-4}alkylcycloalkyl$, or $-C_{0-4}alkylheterocyclyl$, wherein any of the rings is optionally substituted with 1-3 independent halogen, cyano, $C_{1-4}alkyl$, fluoromethyl, difluoromethyl, trifluoromethyl, $-C_{0-4}alkylNHC(O)O(C_{1-4}alkyl)$, $-C_{0-4}alkylNR^7R^8$, $-C(O)R^9$, $C_{1-4}alkoxyC_{0-4}alkyl$ -, $-COOC_{0-4}alkyl$, $-C_{0-4}alkylNHC(O)R^9$, $-C_{0-4}alkylC(O)N(R^{10})_2$, $-C_{1-4}alkoxyC_{1-4}alkoxy$, hydroxy $C_{0-4}alkyl$ -, $-NHSO_2R^{10}$, $-SO_2(C_{1-4}alkyl)$, $-SO_2NR^{11}R^{12}$, 5- to 6-membered heterocyclyl, phenyl $C_{0-2}alkoxy$, or phenyl $C_{0-2}alkyl$ substituents, wherein phenyl is optionally substituted with 1-2 independent halogen, cyano, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-SO_2C_{1-4}alkyl$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents, or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo ($=O$) substituent;

or R^3 is $-NR^4(-C_{0-4}alkylR^5)$;

R^4 is $C_{0-3}alkyl$, $-C_{2-3}alkyl-NR^7R^8$, $C_{3-6}cycloalkyl$ optionally substituted by hydroxy $C_{0-4}alkyl$ - further optionally substituted by hydroxy, $C_{1-2}alkoxyC_{2-4}alkyl$ -, or $C_{1-2}alkyl-S(O)_n-C_{2-3}alkyl$;

n is 0, 1, or 2;

R^5 is hydrogen, hydroxy $C_{2-3}alkyl$ -, $C_{1-2}alkoxyC_{0-4}alkyl$ -, or aryl, hetaryl, or heterocyclyl;

wherein a heterocyclic nitrogen-containing R^5 ring optionally is mono-substituted on the ring nitrogen with $C_{1-4}alkyl$, benzyl, benzoyl, $C_{1-4}alkyl-C(O)$ -, $-SO_2C_{1-4}alkyl$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $C_{1-4}alkoxycarbonyl$, or aryl($C_{1-4}alkoxy$)carbonyl; and wherein the R^5 rings are optionally mono-substituted on a ring carbon with halogen, cyano, $C_{1-4}alkyl-C(O)$ -, $C_{1-4}alkyl-SO_2$ -, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, hydroxy, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, hydroxy $C_{0-4}alkyl$ -, or $C_{0-4}alkylcarbamoyl$ -, provided that no quaternised nitrogen is included; or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo ($=O$) substituent;

R^6 is $C_{1-4}alkyl$, aryl, or hetaryl;

R^7 and R^8 are independently $C_{0-4}alkyl$, $C_{3-6}cycloalkyl$, or $CO(C_{1-4}alkyl)$;

R^9 is $C_{1-4}alkyl$, or $C_{3-6}cycloalkyl$;

R^{10} is $C_{0-4}alkyl$, or $C_{3-6}cycloalkyl$; and

R^{11} and R^{12} are independently $C_{0-4}alkyl$ or together with the nitrogen to which they are attached may form a 4- to 6-membered heterocycle;

provided there are no nitrogen-oxygen, nitrogen-nitrogen, oxygen-oxygen or nitrogen-halogen bonds in the grouping $-Y-Z-R^3$.

The molecular weight of the compounds of formula (I) is preferably less than 800, more preferably less than 600.

X_3 is preferably N.

Y is preferably $-C(O)$ - or $-S(O)_2$ -.

Z is preferably a C₁₋₄alkylene, oxygen, -(CH₂)_mO-, -NR- or a bond. More preferably Z is a bond.

R is preferably C₀₋₄alkyl.

R¹ and R^{1'} are preferably each independently, hydrogen, halogen or cyano. More preferably one of R¹ and R^{1'} is hydrogen and the other is halogen, e.g. chloro. More preferably one of R¹ and R^{1'} is hydrogen and the other is 5-chloro.

R² is preferably C₀₋₄alkyl. More preferably R² is hydrogen.

R³ is preferably hydrogen, -NR⁴(-C₀₋₄alkylR⁵), aryl, hetaryl, or heterocyclyl wherein any of the rings is optionally substituted as described above for formula (I).

R⁴ is preferably hydrogen.

Specific compounds of the invention which may be mentioned are those included in the examples and pharmaceutically acceptable salts thereof.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in formula (I) is selected from the preferred, more preferred, most preferred, especially or particularly listed groups for each variable. Therefore, this invention is intended to include all combinations of preferred, more preferred, most preferred, especially and particularly listed groups.

As used herein, unless stated otherwise, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

As used herein, for example, "C₀₋₄alkyl" is used to mean an alkyl having 0-4 carbons — that is, 0, 1, 2, 3, or 4 carbons in a straight or branched configuration. An alkyl having no carbon is hydrogen when the alkyl is a terminal group. An alkyl having no carbon is a direct bond when the alkyl is a bridging (connecting) group.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and include mono-, bi-, and tricyclic saturated carbocycles, as well as fused and bridged systems. Such fused ring systems can include one ring that is partially or fully unsaturated, such as a benzene ring, to form fused ring systems, such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl and carbocyclic rings include C₃₋₁₀cycloalkyl, e.g. C₃₋₈cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and decahydronaphthalene, adamantane, indanyl, 1,2,3,4-tetrahydronaphthalene and the like.

The term "halogen" includes fluorine, chlorine, bromine, and iodine atoms.

The term "aryl" is well known to chemists. The preferred aryl groups are phenyl and naphthyl, especially phenyl.

The term "hetaryl" is well known to chemists. The term includes 5- or 6-membered heteroaryl rings containing 1-4 heteroatoms chosen from oxygen, sulfur, and nitrogen in which oxygen and sulfur are not next to each other. Examples of such heteroaryl rings are furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

The term "hetaryl" includes hetaryl rings with fused carbocyclic ring systems that are partially or fully unsaturated, such as a benzene ring, to form a benzofused hetaryl. For example, benzimidazole, benzoxazole, benzothiazole, benzofuran, quinoline, isoquinoline, quinoxaline, and the like.

Unless otherwise stated, the terms "heterocyclic ring" and "heterocyclyl" are equivalent, and include 4–8-membered saturated or partially saturated rings containing one or two heteroatoms chosen from oxygen, sulfur, and nitrogen. The sulfur and oxygen heteroatoms are not directly attached to one another. Any nitrogen heteroatoms in the ring may optionally be substituted with C₁₋₄alkyl. Examples of heterocyclic rings include azetidine, oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocane, thietane, thiazolidine, oxazolidine, oxazetidine, pyrazolidine, isoxazolidine, isothiazolidine, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, *N*-methylpiperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, homopiperazine, morpholine, thiomorpholine, 1,2,3,6-tetrahydropyridine and the like. Other examples of heterocyclic rings include the oxidized forms of the sulfur-containing rings. Thus, tetrahydrothiophene-1-oxide, tetrahydrothiophene-1,1-dioxide, thiomorpholine-1-oxide, thiomorpholine-1,1-dioxide, tetrahydrothiopyran-1-oxide, tetrahydrothiopyran-1,1-dioxide, thiazolidine-1-oxide, and thiazolidine-1,1-dioxide are also considered to be heterocyclic rings. The term "heterocyclic" also includes fused ring systems and can include a carbocyclic ring that is partially or fully unsaturated, such as a benzene ring, to form benzofused heterocycles. For example, 3,4-dihydro-1,4-benzodioxine, tetrahydroquinoline, tetrahydroisoquinoline and the like.

Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above formula (I) is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of formula (I) and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When a tautomer of the compound of formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically drawn or stated otherwise.

When the compound of formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric,

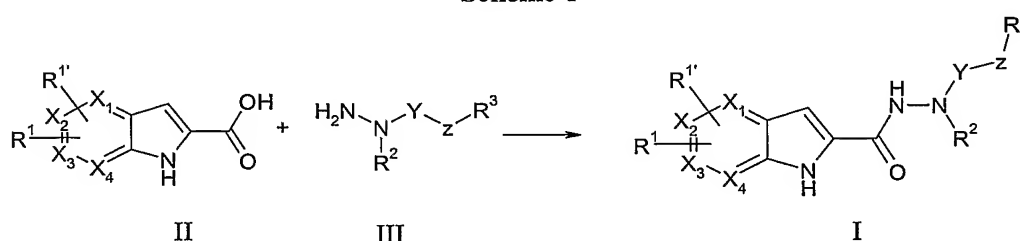
ferrous, lithium, magnesium, potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, *p*-toluenesulfonic acid and the like.

Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure especially at least 98% pure (% are on a weight for weight basis).

The compounds of formula (I) can be prepared as outlined in Scheme 1 below wherein R^1 , $R^{1'}$, R^2 , R^3 , X_1 , X_2 , X_3 , X_4 , Y and Z are as defined above for formula (I):

Scheme 1



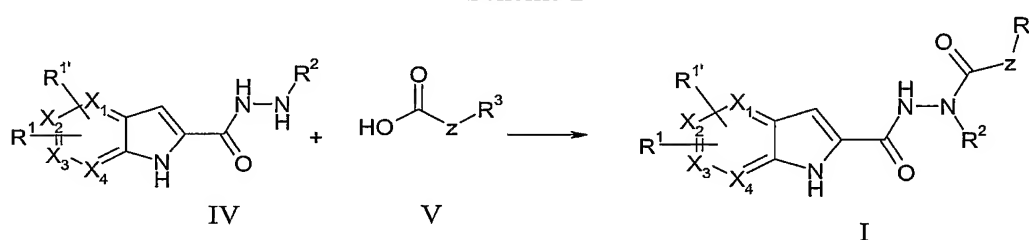
According to Scheme 1, the compounds of formula (I) may be prepared by coupling the appropriate pyrrolopyridine-2-carboxylic acid of formula (II) with the appropriate hydrazide of formula (III), wherein $Y = C(O)$. Compounds of formula (II) can be obtained by the synthesis described in Scheme 7 below. Compounds of formula (III) are generally commercially available or are readily prepared by known techniques.

Typically, the compound of formula (II) is combined with compounds of formula (III) in the presence of a suitable coupling agent. Examples of suitable coupling reagents are 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride/hydroxybenzotriazole (EDCI / HOBt), 1,1-carbonyldiimidazole (CDI), dicyclohexylcarbodiimide/hydroxybenzotriazole (DCC / HOBt), *O*-(1H-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (R. Knorr *et al.*, *Tetrahedron Lett.*, 1989, 30, 1927–1930) and polymer supported carbodiimide-1-hydroxybenzotriazole (for representative procedures, see for example, Argonaut Technical Note 501 available from Argonaut Technologies, Inc., Foster City, California).

The couplings are performed in an inert solvent, preferably an aprotic solvent at a temperature of about 0°C to about 45°C for about 1 to 72h in the presence of a tertiary amine base such as diisopropylethylamine (DIPEA) or triethylamine. Exemplary solvents include acetonitrile, chloroform, dichloromethane, *N,N*-dimethylformamide (DMF) or mixtures thereof. Use of these coupling agents and appropriate selection of solvents and temperatures are known to those skilled in the art or can be readily determined from the literature. These and other exemplary conditions useful for coupling carboxylic acids are described in Houben-Weyl, Vol XV, part II, E. Wunsch, Ed., G. Thieme Verlag, 1974, Stuttgart, and M. Bodansky, Principles of Peptide Synthesis, Springer-Verlag, Berlin, 1984 and The Peptides, Analysis, Synthesis and Biology (Ed., E. Gross and J. Meienhofer), Vols 1-5, Academic Press NY 1979-1983.

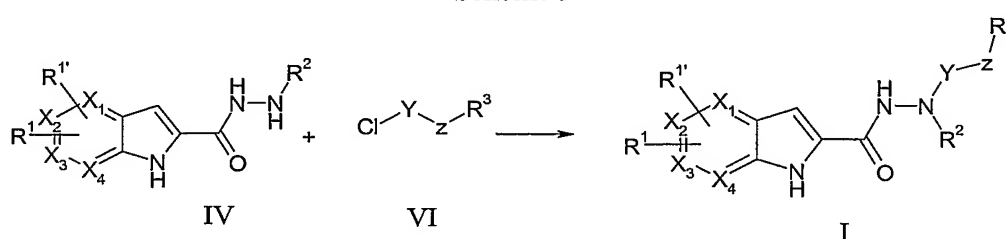
The compounds of formula (I), wherein Y is C(O), may also be prepared according to Scheme 2 by coupling the appropriate hydrazide of formula (IV) with the appropriate carboxylic acid of formula (V). Examples of suitable coupling agents and conditions are as described above. Compounds of formula (IV) can be obtained by the synthesis described in Scheme 9 below. Compounds of formula (V) are commercially available or are readily prepared by known techniques.

Scheme 2



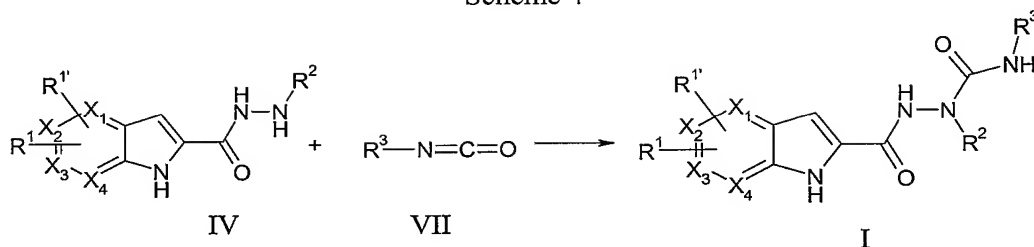
The compounds of formula (I), wherein Y is C(O) or -SO₂-, may be prepared according to Scheme 3 by mixing the appropriate hydrazide of formula (IV) with the appropriate acid chloride or sulfonyl chloride of formula (VI) in pyridine at room temperature, or alternatively in the presence of a tertiary amine base, e.g. diisopropylethylamine in a solvent such as 1,4-dioxane or THF at room temperature. Acid chlorides or sulfonyl chlorides of formula (VI) are commercially available or are readily prepared by known techniques.

Scheme 3



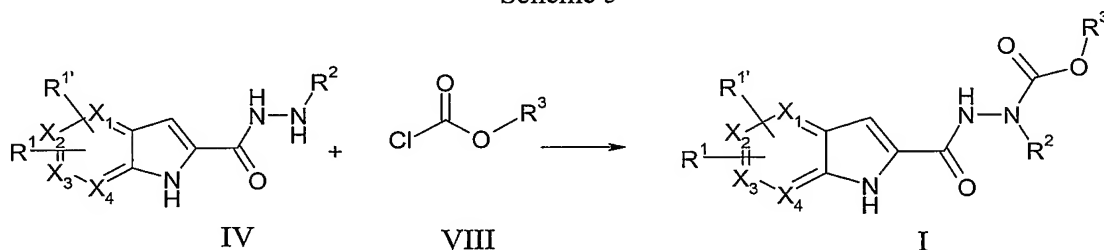
The compounds of formula (I), wherein Y is C(O) and Z is NH, may be prepared according to Scheme 4 by heating the appropriate hydrazide of formula (IV) with the appropriate isocyanate of formula (VII) under reflux in the presence of a tertiary amine base, e.g. diisopropylethylamine in a solvent such as 1,4-dioxane or toluene.

Scheme 4



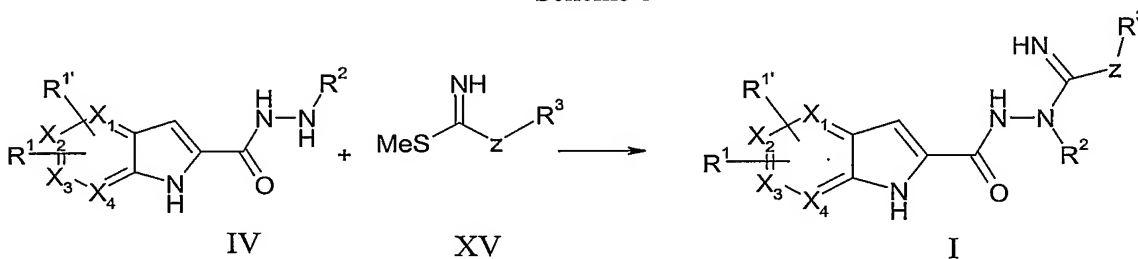
The compounds of formula (I), wherein Y is C(O), and Z is oxygen, may be prepared according to Scheme 5 by mixing the appropriate hydrazide of formula (IV) with the appropriate chloroformate of formula (VIII) in the presence of a tertiary amine base, e.g. triethylamine in a solvent such as dichloromethane.

Scheme 5

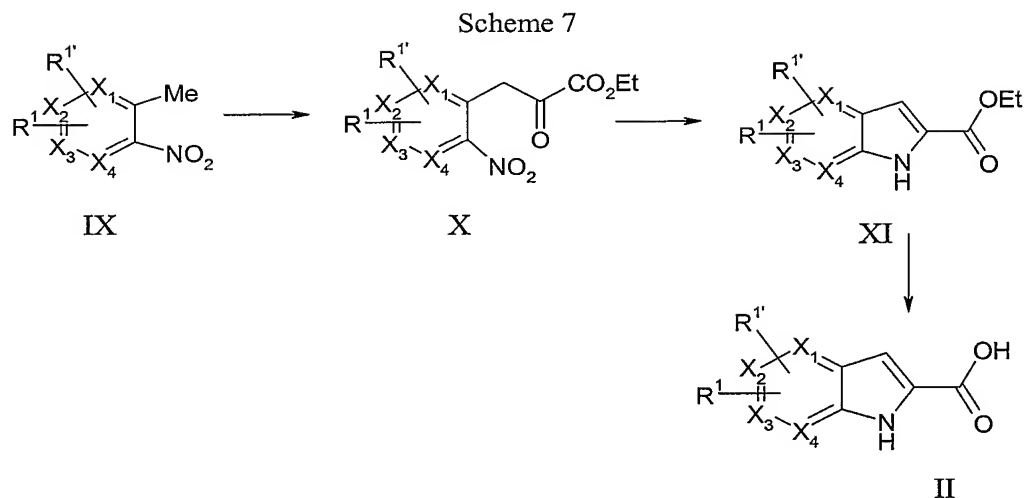


The compounds of formula (I), wherein Y is C(NH), may be prepared according to Scheme 6 by mixing the appropriate hydrazide of formula (IV) with the appropriate thioimide of formula (XV) in a solvent such as ethanol or dimethylformamide.

Scheme 6

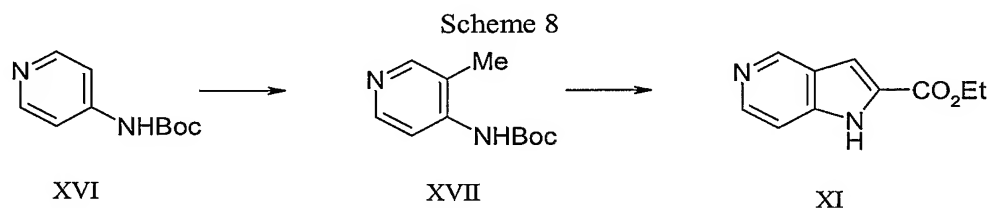


The compounds of formula (II) may be prepared according to Scheme 7. Compounds of formula (X) may be prepared by condensation of *ortho*-methyl nitro compounds of formula (IX) with an oxalate ester in a solvent such as diethyl ether in the presence of a base such as potassium ethoxide or DBU. Compounds of formula (XI) are prepared from compounds of formula (X) under reducing conditions, such as iron powder and ammonium chloride in ethanol at about 70°C, or by hydrogenation in ethanol using palladium catalysis at around 20°C. Compounds of formula (XI) undergo ester hydrolysis using aqueous alkali under standard conditions to give pyrrolopyridine-2-carboxylic acids of formula (II).



This three step process is similar to the Reissert indole synthesis (Reissert, *Chemische Berichte* **1897**, 30, 1030). Conditions for accomplishing this sequence and references thereto, are described in Kermack et al., *J. Chem. Soc.*, **1921**, 119, 1602; Cannon et al., *J. Med. Chem.* **1981**, 24, 238; and Julian et al., in *Heterocyclic compounds*, Vol 3 (Wiley, New York, NY, 1962, R.C. Elderfield, Ed. p 18).

Alternatively, the compounds of formula (XI) wherein X_2 is nitrogen can be prepared as illustrated in Scheme 8.



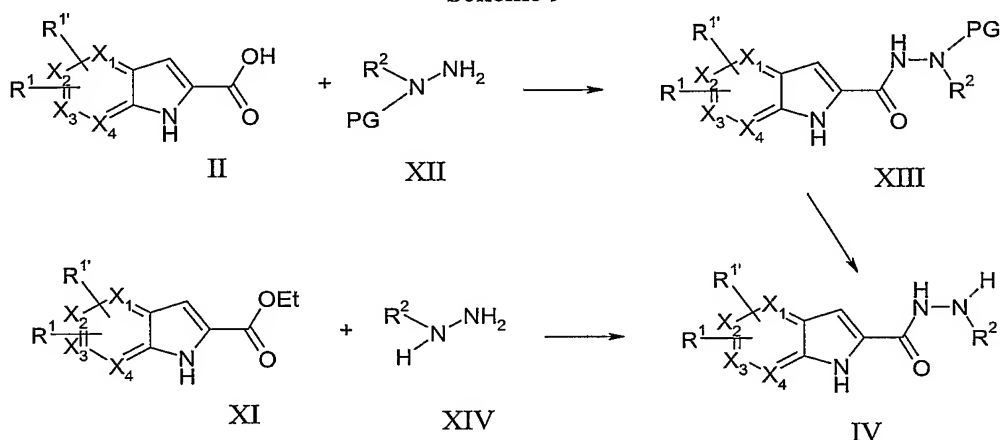
Deprotonation of compounds of formula (XVI) with an organolithium such as *n*-butyllithium in a suitable solvent such as THF, followed by quenching with methyl iodide gives compounds of formula (XVII). Such compounds can undergo further deprotonation with *tert*-butyllithium, in a suitable solvent such as THF, followed by quenching with diethyl oxalate and subsequent heating of the intermediate under reflux in hydrochloric acid, to give compounds of formula (XI).

Further details for the preparation of compounds of formula (II) can be found in WO04/104001 and the examples therein.

Formula (XIII) compounds may be prepared as described in Scheme 9 by coupling of carboxylic acids of formula (II) with hydrazines of formula (XII), wherein PG is a protecting group, e.g. Boc. Examples of suitable coupling agents and conditions are as described above for Scheme 1. Formula (IV) compounds may then be prepared by removal of the protecting group, e.g. where PG is Boc, under acidic conditions using for example trifluoroacetic acid in dichloromethane at temperatures of around 25°C. Formula (II) compounds are made as described above (Scheme 7) or are commercially available. Formula (XII) compounds are commercially available or are readily prepared by known techniques.

Alternatively compounds of formula (IV), wherein R^2 is hydrogen, may be prepared (Scheme 9) by heating an ethyl ester of formula (XI) with compounds of formula (XIV), wherein R^2 is hydrogen, in a solvent such as ethanol under reflux for a period of 3 to 24h.

Scheme 9



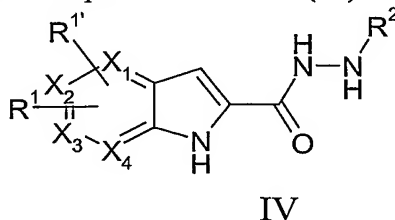
Further details for the preparation of the compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial "split and mix" approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The compounds of formulae (II) and (IV) may be protected in the 1-position e.g. with an arylmethyl, acyl, alkoxycarbonyl, sulfonyl or silyl group. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example, *Protective Groups in Organic Chemistry*, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

Any novel intermediates as defined above are also included within the scope of the invention.

The invention also provides a compound of formula (IV):



wherein R^1 , R^1' , R^2 , X_1 , X_2 , X_3 and X_4 are as defined above for formula (I), or a protected derivative thereof.

As indicated above the compounds of formula (I) are useful as inhibitors of glycogen phosphorylase, for the treatment of conditions such as diabetes, particularly Type II diabetes. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

5 The invention also encompasses a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

10 Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

15 Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by inhibiting glycogen phosphorylase, resulting in the prophylactic or therapeutic treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, e.g. myocardial ischemia, cardioprotection or inhibition of abnormal cell growth, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula (I), or a pharmaceutically acceptable salt thereof.

20 The pharmaceutical compositions may optionally comprise other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

25 In practice, the compounds of formula (I), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous).

30 Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

40 The compounds of formula (I), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

5 In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like
10 may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

15 A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet
20 preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total
25 composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water.
30 A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of
35 sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion
40 medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These

formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient.

Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, diabetes and hyperglycemia may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Similarly, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, atherosclerosis or myocardial ischemia may be effectively treated, or cardioprotection or inhibition of abnormal cell growth achieved, by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of formula (I) may be used in the treatment of diseases or conditions in which glycogen phosphorylase plays a role.

Thus the invention also provides a method for the treatment of a disease or condition in which glycogen phosphorylase plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Diseases or conditions in which glycogen phosphorylase plays a role include diabetes (including Type I and Type II, impaired glucose tolerance, insulin resistance and diabetic complications such as neuropathy, nephropathy, retinopathy and cataracts), hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis, tissue ischemia e.g. myocardial ischemia, cardioprotection and abnormal cell growth e.g. cancer or hyperproliferative disorders.

The invention also provides a method for the treatment of hyperglycemia or diabetes, particularly Type II diabetes, comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the prevention of diabetes in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering to a subject in need thereof an effective prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In the treatment of diabetes, e.g. Type II diabetes, the compounds of the invention are particularly suited to night time dosing, optionally in combination with another antidiabetic agent.

The invention also provides a method for the treatment of hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, or achieving cardioprotection or inhibition of abnormal cell growth, comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the treatment of a condition as defined above.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition as defined above.

In the methods of the invention the term "treatment" includes both therapeutic and prophylactic treatment.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, may be administered alone or in combination with one or more other therapeutically active compounds. The other therapeutically active compounds may be for the treatment of the same disease or condition as the compounds of formula (I) or a different disease or condition. The therapeutically active compounds may be administered simultaneously, sequentially or separately.

The compounds of Formula (I) may be administered with other active compounds for the treatment of diabetes, for example insulin and insulin analogs, sulfonyl ureas and analogs, biguanides, $\alpha 2$ agonists, fatty acid oxidation inhibitors, α -glucosidase inhibitors, β -agonists, phosphodiesterase inhibitors, lipid lowering agents, antiobesity agents, amylin antagonists, lipoxigenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTP1B inhibitors, gluconeogenesis inhibitors, antilypolitic agents, GSK inhibitors, galanin receptor agonists, anorectic agents, CCK receptor agonists, leptin, CRF antagonists or CRF binding proteins.

The compounds of formula (I) may also be administered in combination with thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors or sorbitol dehydrogenase inhibitors.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

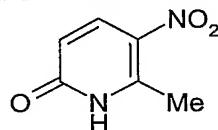
Materials & methods:

Column chromatography was carried out on SiO₂ (40–63 mesh). LCMS data were obtained using a Waters Symmetry 3.5 μ C₁₈ column (2.1 \times 30.0 mm, flow rate = 0.8 mL min⁻¹) eluting with a (5% MeCN in H₂O)–MeCN solution containing 0.1% HCO₂H over 6min & UV detection at 220nm. Gradient information: 0.0–1.2min: 100% (5% MeCN in H₂O); 1.2–3.8min: Ramp up to 10% (5% MeCN in H₂O)–90% MeCN; 3.8–4.4min: Hold at 10% (5% MeCN in H₂O)–90% MeCN; 4.4–5.5min: Ramp up to 100% MeCN; 5.5–6.0min: Return to 100% (5% MeCN in H₂O). The mass spectra were obtained employing an electrospray ionisation source in the positive (ES⁺) ion mode. Mass directed purification was performed on a Micromass Platform LC with cone voltage 30v, employing an electrospray ionisation source in the positive (ES⁺) ion mode, Waters 996 Photodiode Array Detector (210–390nm), Xterra Prep MS, C₁₈, 5 μ 19x50mm columns, and a mobile Phase of MeCN + 0.1% Formic Acid / H₂O+5%MeCN+0.1% Formic Acid. NMR spectra were acquired at 27°C on a Varian Mercury 400 spectrometer operating at 400 MHz or on a Bruker AMX2 500 spectrometer operating at 500MHz.

Abbreviations & acronyms:

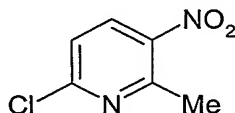
CDI: 1,1-carbonyldiimidazole; DIPEA: *N,N*-Diisopropylethylamine; DMF: *N,N*-Dimethylformamide; DMSO: Dimethylsulfoxide; EDCl: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; GP: Glycogen Phosphorylase; Glc: Glucose; G6P: Glucose-6-phosphate; G6PDH: Glucose-6-phosphate dehydrogenase; HATU: *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HOBt: 1-Hydroxybenzotriazole; PS: Polymer supported; rt: room temperature; RT: Retention time; THF: Tetrahydrofuran.

INTERMEDIATES:

Preparation 1: 6-Methyl-5-nitro-1*H*-pyridin-2-one

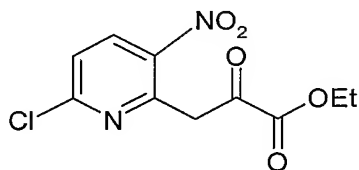
The title compound was prepared according to the method of Baumgarten and Su., (*J. Am. Chem. Soc.*, **1952**, 74, 3828). δ_{H} (d₆ DMSO): 2.62 (3H, s), 6.28 (1H, d), 8.10 (1H, d).

Preparation 2: 2-Chloro-6-methyl-4-nitropyridine



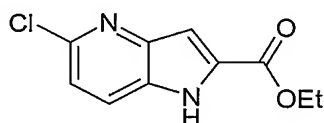
A suspension of 6-methyl-5-nitro-1*H*-pyridin-2-one (Preparation 1, 3.53g, 22.9mmol) in phosphorous oxychloride (20mL) was heated to 115°C for 3h then allowed to cool to rt. The phosphorous oxychloride was removed *in vacuo* and the residue poured into iced water (100mL). The mixture was quenched by addition of saturated sodium bicarbonate solution then the aqueous mixture was extracted with ethyl acetate (3 x 100mL). The combined organics were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo* to give the title compound. δ_{H} (CDCl₃): 2.86 (3H, s), 7.36 (1H, d), 8.27 (1H, d).

Preparation 3: 3-(2-Chloro-5-nitropyridin-6-yl)-2-oxopropionic acid ethyl ester



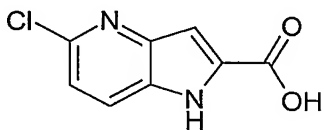
To a solution of potassium ethoxide (134mg, 1.59mmol) in diethyl ether (5mL) and ethanol (1mL) was added diethyl oxalate (218μL, 1.59mmol) in one portion and the resulting solution was stirred for 30min at rt. 2-Chloro-6-methyl-5-nitropyridine (Preparation 2, 250mg, 1.45mmol) was added as a suspension in diethyl ether (2mL) and stirring was continued for 17h at rt. The mixture was filtered on a sinter, washing with cold diethyl ether. The collected precipitate was dissolved in glacial acetic acid then evaporated to dryness *in vacuo* to give the title compound. δ_H (CDCl₃): 1.40 (3H, t), 4.38 (2H, q), 7.33 (1H, d), 7.37 (1H, s), 8.40 (1H, d).

Preparation 4: 5-Chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid ethyl ester



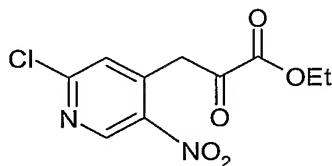
To a solution of 3-(2-chloro-5-nitropyridin-6-yl)-2-oxopropionic acid ethyl ester (Preparation 3, 1.53g, 5.6mmol) in THF (65mL) and ethanol (30mL) was added saturated aqueous ammonium chloride solution (30mL) and the suspension was vigorously stirred at rt. Iron powder (1.95g, 34.8mmol) was added portionwise and the mixture was heated under reflux for 2h then allowed to cool prior to filtration through a celite plug, and washed with warm THF. The mixture was concentrated under reduced pressure to give an aqueous suspension, which was filtered through a sinter, washing with water. The wet solid was washed with methanol and dried. The residue was adsorbed onto silica gel and purified *via* flash chromatography eluting with ethyl acetate/hexane (1:19) to give the title compound. δ_H (CD₃OD): 1.42 (3H, t), 4.42 (2H, q), 7.15 (1H, s), 7.30 (1H, d), 7.89 (1H, d); m/z (ES⁺) = 225.03 [$M + H$]⁺, RT = 3.32min.

Preparation 5: 5-Chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid



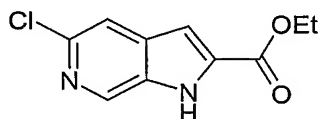
To a stirred solution of 5-chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid ethyl ester (Preparation 4, 151mg, 0.67mmol) in ethanol (10mL) was added sodium hydroxide (0.35mL, 2M) and the stirred solution was heated to 70°C for 2h. The reaction mixture was allowed to cool to rt and left to stand for 16h. The pH was adjusted to 4 by addition of glacial acetic acid, the solvents removed *in vacuo* to give a white solid, which was suspended in dichloromethane and filtered through a sinter, washing with additional dichloromethane. The filter cake was then washed with ethyl acetate (3 x 30mL) and dried to give the title compound. δ_H (CD₃OD): 6.97 (1H, s), 7.17 (1H, d), 7.83 (1H, d); m/z (ES⁺) = 197 [$M + H$]⁺; RT = 2.82min.

Preparation 6: 3-(2-Chloro-5-nitropyridin-4-yl)-2-oxopropionic acid ethyl ester



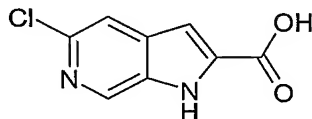
To a solution of potassium ethoxide (1.46g, 17.4mmol) in diethyl ether (80mL) and ethanol (10mL) under an argon atmosphere was added diethyl oxalate (2.4mL, 17.4mmol) and the mixture was stirred at rt for 30min. A solution of 2-chloro-4-methyl-5-nitropyridine (3.0g, 17.4mmol) in diethyl ether (20mL) was added resulting in the formation of a dark green precipitate. The reaction was stirred at rt for 15h, cooled to 0°C, filtered and washed with cold diethyl ether to give a dark green solid. The solid was dissolved in water (200mL) and acidified to pH 4 with acetic acid to give a precipitate. The solid was collected by filtration and dried to give the title compound. m/z (ES^+) = 273 [$M + H$] $^+$.

Preparation 7: 5-Chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid ethyl ester



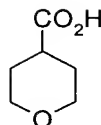
3-(2-Chloro-5-nitropyridin-4-yl)-2-oxopropionic acid ethyl ester (Preparation 6, 3.0g, 11.0mmol) was dissolved in ethanol (100mL) and THF (50mL). Iron powder (3.7g, 66.0mmol) and saturated ammonium chloride solution (50mL) were added and the mixture was heated under reflux for 2h. The mixture was cooled, filtered through celite and washed several times with ethyl acetate. The organic layers were combined, washed with brine (100mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound. δ_H (CD_3OD): 1.42 (3H, t), 4.44 (2H, q), 7.15 (1H, s), 7.70 (1H, s), 8.59 (1H, s); m/z (ES^+) = 225 [$M + H$] $^+$.

Preparation 8: 5-Chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid



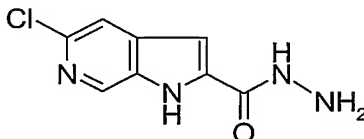
To a solution of 5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid ethyl ester (Preparation 7, 1.78g, 7.9mmol) in ethanol (70mL) was added sodium hydroxide solution (5.2mL, 2M, 10.3mmol) and the mixture was heated under reflux for 2h. The solvent was removed *in vacuo* and the solid dissolved in water (150mL) and acidified to pH 4 with acetic acid to give the title compound as a solid that was isolated by filtration. δ_H (CD_3OD): 7.13 (1H, s), 7.68 (1H, s), 8.58 (1H, s); m/z (ES^+) = 197 [$M + H$] $^+$.

Preparation 9: Tetrahydropyran-4-carboxylic acid



This compound was prepared by hydrolysis of the methyl ester according to the method of Spiegler and Goetz, *Ger. Offen.* (1987) DE 3536956 A1.

Preparation 10: 5-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide



Route 1

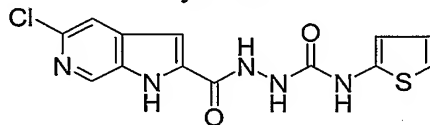
N'-(*tert*-Butyloxycarbonyl)-5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide (EXAMPLE 25, 930mg, 2.99mmol) was suspended in a mixture of dichloromethane and trifluoroacetic acid (1:1, 20mL). After 2h the mixture was concentrated *in vacuo* and the oily residue was dissolved in water (200mL). The aqueous layer was washed with ethyl acetate (2 x 50mL) and concentrated *in vacuo* to give the title compound as its trifluoroacetic acid salt. δ_H (d_6 DMSO) 7.36 (1H, s), 7.83 (1H, s), 8.66 (1H, s), 9.3-10.8 (3H, br s), 11.8-12.2 (1H, br s), 12.6 (1H, s); m/z (ES^+) = 211 [$M + H$] $^+$; RT = 0.42min.

Route 2

To a solution of 5-chloro-1*H*-pyrrolo [2,3-*c*] pyridine-2-carboxylic acid ethyl ester (Preparation 7, 880mg, 3.91mmol) in ethanol (30mL) was added hydrazine monohydrate (4.0mL, 78.22mmol). The resulting solution was refluxed at 90°C for 5h. The reaction mixture was cooled to rt and the precipitate was filtered and dried to give the title compound. m/z (ES^+) = 211 [$M + H$] $^+$; RT = 1.65min.

EXAMPLE 1

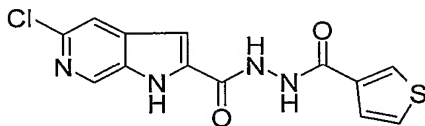
5-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid *N'*-(thiophene-2-yl-aminocarbonyl) hydrazide



DIPEA (53 μ L, 0.31mmol) and thienyl isocyanate (40 μ L, 0.32mmol) were added to a suspension of 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide trifluoroacetic acid salt (Preparation 10 – route 1, 101mg, 0.31mmol) in a mixture of toluene and 1,4-dioxane (10mL, 1:1). After stirring the mixture at 100°C for 12h, the reaction was allowed to cool to rt and the solvent was removed. The remaining oily residue was purified by flash chromatography on silica gel (toluene/acetone : 2/1) to give the title compound. δ_H ($CDCl_3$): 6.60 (1H, d), 6.78 (1H, m), 6.84 (1H, d), 7.26 (1H, d), 7.82 (1H, s), 8.61 (2H, m), 9.97 (1H, s); m/z (ES^+) = 336 [$M + H$] $^+$; RT = 2.97min.

EXAMPLE 2

Thiophene-3-carboxylic acid *N'*-(5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carbonyl)hydrazide



To a solution of 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide trifluoroacetic acid salt (Preparation 10 – route 1, 0.110g, 0.34mmol) in DMF (3mL) was added DIPEA (170.0μL, 1.02mmol). To the stirred solution, HOBt (0.046g, 0.34mmol), EDCI (0.078g, 0.41mmol), DIPEA (120.0μL, 0.68mmol) and thiophene-3-carboxylic acid (0.044g, 0.34mmol) were added. The reaction mixture was stirred at rt for 16h and then concentrated *in vacuo* to give an oil. On addition of ethyl acetate to the oil, a solid precipitated. The solid was filtered and dried to give the title compound. *m/z* (*ES*⁺) = 321[*M* + *H*]⁺; RT = 2.84min.

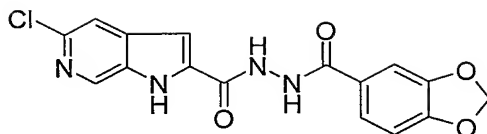
The coupling of the appropriate carboxylic acid with 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide, outlined in EXAMPLE 2, was also employed to prepare the compounds listed in Table 1 below.

Table 1

EX.	Structure	Name	RT	<i>m/z</i> (<i>ES</i> ⁺)
3		Furan-3-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.75	305
4		Tetrahydrofuran-3-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.59	309
5		1 <i>H</i> -Pyrrole-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.77	304
6		Benzoic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	3.02	315

EXAMPLE 7

Benzo[1,3]dioxole-5-carboxylic acid *N'*-(5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carbonyl)hydrazide



To a solution of 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide (Preparation 10 – route 2, 0.100g, 0.48mmol) in DMF (4mL) was added HOBt (0.064g, 0.48mmol), EDCI (0.110g, 0.58mmol), DIPEA (200μL, 0.96mmol) and piperonylic acid (0.079g, 0.48mmol). The reaction mixture was stirred at rt for 16h. The reaction mixture was poured into water (75mL) and extracted with ethyl acetate (2 x 150mL). The combined organic extract was washed with saturated sodium chloride (75mL), dried (MgSO₄) and concentrated *in vacuo* to give a solid. The solid obtained was purified by recrystallisation from methanol to give the title compound. *m/z* (ES⁺) = 359 [*M* + H]⁺; RT = 2.92min.

The coupling of the appropriate carboxylic acid with 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid hydrazide, outlined above in EXAMPLE 7 was also employed to prepare the compounds listed in Table 2 below.

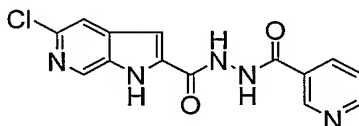
Table 2

EX.	Structure	Name	RT	<i>m/z</i> (ES ⁺)
8		Tetrahydropyran-4-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>]pyridine-2-carbonyl) hydrazide	2.49	323
9		Cyclopropane carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.42	279
10		4-Methylbenzoic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>]pyridine-2-carbonyl) hydrazide	2.95	329
11		2(<i>S</i>)-[<i>N'</i> -(5-Chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>] pyridine-2-carbonyl)-hydrazinocarbonyl] pyrrolidine-1-carboxylic acid tert-butyl ester	3.01	408
12		Pyrrolidine-2(<i>S</i>)-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo [2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	0.65	308

EX.	Structure	Name	RT	m/z (ES ⁺)
13		3(S)- N'-(5-Chloro-1H-pyrrolo [2,3-c] pyridine-2-carbonyl)-hydrazinocarbonyl] pyrrolidine-1-carboxylic acid tert-butyl ester	3.32	408
14		Pyrrolidine-3(S)-carboxylic acid N'-(5-chloro-1H-pyrrolo [2,3-c]pyridine-2-carbonyl)hydrazide	2.27	308

EXAMPLE 15

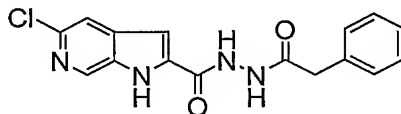
Pyridine-3-carboxylic acid N'-(5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carbonyl)hydrazide



To a solution of nicotinic acid hydrazide (35mg, 0.25mmol) in DMF (5mL) was added triethylamine (88μL, 0.64mmol), 5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (Preparation 8, 50mg, 0.25mmol), HOBt (34mg, 0.25mmol) and EDCI (50mg, 0.28mmol). The mixture was allowed to stir at rt for 16h. The solvent was removed *in vacuo* and the residue was partitioned between water (100mL) and ethyl acetate (100mL). The organic layer was dried (MgSO₄) and concentrated *in vacuo* to give an oil, which was purified by flash chromatography on silica gel (dichloromethane/methanol, 9/1) to give the title compound. m/z (ES⁺) = 316 [M + H]⁺; RT = 2.62min.

EXAMPLE 16

5-Chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid N'-phenylacetylhydrazide



To a solution of 5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (Preparation 8, 50mg, 0.25mmol) in DMF (10mL) was added DIPEA (89μL, 0.51mmol), HOBt (34mg, 0.25mmol), EDCI (63mg, 0.33mmol) and phenylacetic acid hydrazide (38mg, 0.25mmol) and the mixture was stirred at rt for 72h. The reaction mixture was partitioned between water (50mL) and ethyl acetate (3 x 30mL). The combined organics were washed with brine (20mL), dried (MgSO₄) and concentrated *in vacuo*. The crude material was chromatographed on silica gel eluting with methanol / dichloromethane (1:19) to give the title compound. m/z (ES⁺) = 329 [M + H]⁺; RT = 3.07min.

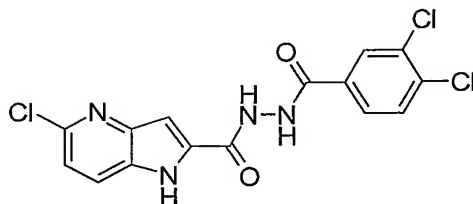
The coupling of the appropriate hydrazide with 5-chloro-1*H*-pyrrolo[2,3-*c*] pyridine-2-carboxylic acid, outlined in EXAMPLE 16, was also employed to prepare the compounds listed in Table 3 below.

Table 3

EX.	Structure	Name	RT (min)	m/z (ES ⁺)
17		5-Chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carboxylic acid <i>N'</i> -(4-chlorophenylaminocarbonyl)hydrazide	3.30	364
18		3,4-Dichlorobenzoic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	3.40	385
19		2,3-Dihydrobenzo[1,4]dioxine-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.95	329
20		2-Chlorophenoxy acetyl <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	3.30	379
21		Thiophene-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.95	321
22		Furan-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	2.88	305
23		1-Methyl-1 <i>H</i> -pyrrole-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridine-2-carbonyl)hydrazide	3.05	318

EXAMPLE 24

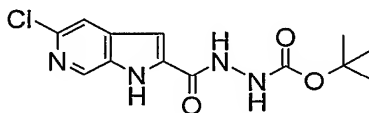
3,4-Dichlorobenzoic acid *N'*-(5-chloro-1*H*-pyrrolo[3,2-*b*]pyridine-2-carbonyl)hydrazide



To a solution of 5-chloro-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylic acid (Preparation 5, 20.0mg, 0.10mmol) in DMF (5mL) was added 3,4-dichlorobenzoic acid hydrazide (23mg, 0.11mmol), DIPEA (19.5μL, 0.11mmol) and HOBt (14.0mg, 0.10mmol). The resulting solution was stirred for 5min prior to the addition of EDCI (23mg, 1.20mmol). The reaction mixture was stirred for 16hr at rt then partitioned between water (10mL) and dichloromethane (20mL) on a hydrophobic frit. The aqueous phase was extracted with a further portion of dichloromethane (30mL) and the combined organics were concentrated *in vacuo*. Trituration of the resulting residue with ethyl acetate / dichloromethane gave the title compound. δ_H (d_6 DMSO): 12.25 (1H, s), 10.83 (2H, d), 8.17 (1H, s), 7.55 – 7.97 (3H, m), 7.38 (1H, s), 7.26 (1H, d); m/z (ES^+) = 383 [$M + H$] $^+$; RT = 3.37min.

EXAMPLE 25

5-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid *N'*-(*tert*-butoxycarbonyl)hydrazide



To a solution of 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid (Preparation 8, 2.05g, 10.4mmol) in DMF (30mL), *tert*-butyl carbazate (1.38g, 10.4mmol), DIPEA (3.5mL, 20.4mmol), HOBt (1.58g, 10.3mmol) and EDCI (2.54g, 13.3mmol) were added successively. The resulting solution was stirred for 12h at rt before adding water and brine (1:1, 200mL). The solution was extracted with ethyl acetate (4 x 50mL) and the combined organic layers were washed with dilute hydrochloric acid (1N, 50mL), dilute sodium hydroxide solution (1N, 50mL) and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a solid residue, which was purified by flash chromatography on silica gel (hexane/ethyl acetate, 1: 3) to give the title compound. δ_H ($CDCl_3$): 1.42 (9H, s), 7.19 (1H, s), 7.78 (1H, s), 8.60 (1H, s), 9.28 (1H, br s).

The biological activity of the compounds of the invention may be tested in the following assay systems:

In vitro GP activity

Materials:

α -D-Glucose-1-Phosphate (disodium salt), Glycogen, D-Glucose, Malachite Green Hydrochloride, Ammonium Molybdate tetrahydrate, BSA, HEPES and rabbit muscle phosphorylase *a* (P1261) were purchased from Sigma. All other reagents were analytical grade.

Method

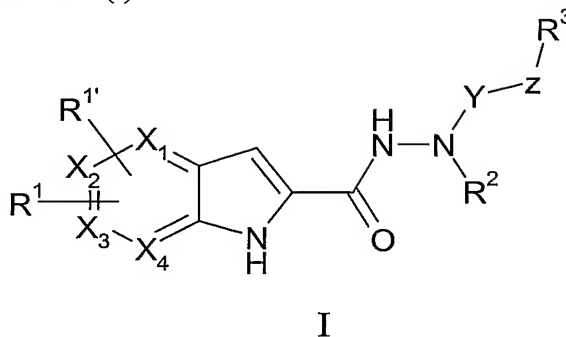
Glycogen phosphorylase assay *in vitro*:

An assay for glycogen phosphorylase activity in the reverse direction was developed based on the method described by Engers *et al.*, *Can. J. Biochem.*, 1970, 48, 746-754]. Rabbit muscle glycogen phosphorylase α (Sigma) was reconstituted at a stock concentration of 100 μ g/mL in 25mM Tris/HCl. The pH was measured in a 96-well plate in a final volume of 100 μ L containing 50mM Hepes pH 7.2, 7.5mM glucose, 0.5mM glucose-1-phosphate and 1mg/mL glycogen. After incubation at 30°C for 30min, the inorganic phosphate released from glucose-1-phosphate was measured by the addition of 150 μ L of malachite green/molybdate solution prepared as follows: 5mL of 4.2% ammonium molybdate in 4N HCl, 15mL of 0.045% malachite green, 50 μ L of Tween 20. Following a 30min incubation at rt, the absorbance was measured at 620nm. For IC₅₀ determination, 10 μ L of a serial dilution of compound (100 μ M to 0.004 μ M) in DMSO was added to each reaction in duplicate with the equivalent concentration of DMSO added to the control uninhibited reaction. Dose response curves were then obtained by plotting % inhibition versus log₁₀ compound concentration. IC₅₀ is defined as the concentration of compound achieving 50% inhibition under the assay conditions described.

Examples of compounds of the present invention demonstrated efficacy in the above assay with IC₅₀ results in the range of better than 100 μ M.

CLAIMS:

1. A compound of formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

one of X₁, X₂, X₃ and X₄ is N and the others are C;

Y is -C(O)-, -S(O)₂-, or -C(NH)-;

Z is C₁₋₄alkylene, oxygen, -(CH₂)_mO-, -O(CH₂)_m-, -NR-, -(CH₂)_mNR-,
-NR(CH₂)_m-, -(CH₂)_mS(O)₂-, or a bond;

m is 1, 2, 3, or 4;

R is C₀₋₄alkyl, C₀₋₄alkylaryl, or C₀₋₄alkylhetaryl;

R¹ and R^{1'} are each independently, halogen, hydroxy, cyano, C₀₋₄alkyl, C₁₋₄alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, or ethynyl;

R² is C₀₋₄alkyl, COOR⁶, COR⁶, C₁₋₄alkoxyC₁₋₄alkyl-, hydroxyC₁₋₄alkyl-, cycloalkylC₀₋₄alkyl-, arylC₀₋₄alkyl-, or hetarylC₀₋₄alkyl-, wherein any of the aryl or hetaryl rings are optionally substituted with 1-2 independent halogen, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, -N(C₀₋₄alkyl)(C₀₋₄alkyl), -SO₂C₁₋₄alkyl, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents;

R³ is hydrogen, -COOC₀₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkyl, arylC₁₋₄alkylthio-, -C₀₋₄alkylaryl, -C₀₋₄alkylhetaryl, -C₀₋₄alkylcycloalkyl, or -C₀₋₄alkylheterocyclyl, wherein any of the rings is optionally substituted with 1-3 independent halogen, cyano, C₁₋₄alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, -C₀₋₄alkylNHC(O)O(C₁₋₄alkyl), -C₀₋₄alkylNR⁷R⁸, -C(O)R⁹, C₁₋₄alkoxyC₀₋₄alkyl-, -COOC₀₋₄alkyl, -C₀₋₄alkylNHC(O)R⁹, -C₀₋₄alkylC(O)N(R¹⁰)₂, -C₁₋₄alkoxyC₁₋₄alkoxy, hydroxyC₀₋₄alkyl-, -NHSO₂R¹⁰, -SO₂(C₁₋₄alkyl), -SO₂NR¹¹R¹², 5- to 6-membered heterocyclyl, phenylC₀₋₂alkoxy, or phenylC₀₋₂alkyl substituents, wherein phenyl is optionally substituted with 1-2 independent halogen, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, -N(C₀₋₄alkyl)(C₀₋₄alkyl), -SO₂C₁₋₄alkyl, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents, or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo (=O) substituent;

or R³ is -NR⁴(-C₀₋₄alkylR⁵);

R⁴ is C₀₋₃alkyl, -C₂₋₃alkyl-NR⁷R⁸, C₃₋₆cycloalkyl optionally substituted by hydroxyC₀₋₄alkyl- further optionally substituted by hydroxy, C₁₋₂alkoxyC₂₋₄alkyl-, or C₁₋₂alkyl-S(O)_n-C₂₋₃alkyl-;

n is 0, 1, or 2;

R⁵ is hydrogen, hydroxyC₂₋₃alkyl-, C₁₋₂alkoxyC₀₋₄alkyl-, or aryl, hetaryl, or heterocyclyl;

wherein a heterocyclic nitrogen-containing R⁵ ring optionally is mono-substituted on the ring nitrogen with C₁₋₄alkyl, benzyl, benzoyl, C₁₋₄alkyl-C(O)-, -SO₂C₁₋₄alkyl, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), C₁₋₄alkoxycarbonyl, or aryl(C₁₋₄alkoxy)carbonyl; and wherein the R⁵ rings are optionally mono-substituted on a ring carbon with halogen, cyano, C₁₋₄alkyl-C(O)-, C₁₋₄alkyl-SO₂-, C₁₋₄alkyl, C₁₋₄alkoxy, hydroxy, -N(C₀₋₄alkyl)(C₀₋₄alkyl), hydroxyc₀₋₄alkyl-, or C₀₋₄alkylcarbamoyl-, provided that no quaternised nitrogen is included; or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo (=O) substituent;

R⁶ is C₁₋₄alkyl, aryl, or hetaryl;

R⁷ and R⁸ are independently C₀₋₄alkyl, C₃₋₆cycloalkyl, or CO(C₁₋₄alkyl);

R⁹ is C₁₋₄alkyl, or C₃₋₆cycloalkyl;

R¹⁰ is C₀₋₄alkyl, or C₃₋₆cycloalkyl; and

R¹¹ and R¹² are independently C₀₋₄alkyl or together with the nitrogen to which they are attached may form a 4- to 6-membered heterocycle;

provided there are no nitrogen-oxygen, nitrogen-nitrogen, oxygen-oxygen or nitrogen-halogen bonds in the grouping -Y-Z-R³.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X₃ is N.

3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X₁ is N.

4. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Y is -C(O)- or -S(O)₂-.

5. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Z is C₁₋₄alkylene, oxygen, -(CH₂)_mO-, -NR- or a bond.

6. A compound according to any one of the preceding claims 1, or a pharmaceutically acceptable salt thereof, wherein R¹ and R^{1'} are each independently, hydrogen or halogen.

7. A compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein one of R¹ and R^{1'} is hydrogen and the other is 5-chloro.

8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R² is hydrogen.

9. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen, -NR⁴R⁵, -NR⁴(-C₁₋₄alkylR⁵), aryl, hetaryl, or heterocyclyl wherein any of the rings is optionally substituted as defined in claim 1.

10. A compound of formula (I) as defined in any one of Examples 1 to 25, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

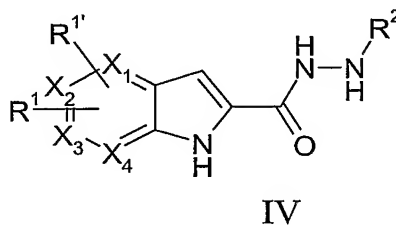
12. A method for the treatment of a disease or condition in which glycogen phosphorylase plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.

13. A method for the treatment of hyperglycemia or diabetes comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.

14. A method for the prevention of diabetes in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering to a subject in need thereof an effective prophylactic amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.

15. A method for the treatment of hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, or achieving cardioprotection or inhibition of abnormal cell growth, comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.

16. A compound of formula (IV):



wherein R¹, R¹', R², X₁, X₂, X₃ and X₄ are as defined in claim 1, or a protected derivative thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/000885

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 2004/104001 A (OSI PHARMACEUTICALS, INC; BRADLEY, STUART, EDWARD; KRULLE, THOMAS, MAR) 2 December 2004 (2004-12-02) cited in the application abstract examples claims	1-16
Y	WO 03/037864 A (JAPAN TOBACCO INC; NAKAMURA, TAKESHI; TAKAGI, MASAKI; UEDA, NOBUHISA) 8 May 2003 (2003-05-08) cited in the application abstract examples claims	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

24 June 2005

Date of mailing of the international search report

01/07/2005

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/000885

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2005/000885

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004104001 A	02-12-2004	WO 2004104001 A2	02-12-2004
WO 03037864 A	08-05-2003	CA 2465382 A1	08-05-2003
		EP 1452526 A1	01-09-2004
		WO 03037864 A1	08-05-2003
		JP 2003201279 A	18-07-2003
		US 2005054696 A1	10-03-2005